Housestaff Manual

July 2024 - June 2025

Department of Medicine
Massachusetts General Hospital
Harvard Medical School
Boston, MA

Editors
Elizabeth Gay, MD
Noemie Levy, MD

It is an honor to present the **30th Edition** of the **MGH Department of Medicine Housestaff Manual**. We submit this manual, which we view as a great tradition of the Internal Medicine Residency Program, to function as a resource for medical residents and other clinicians at MGH. We hope that it exemplifies the energy, compassion, and spirit of growth with which MGH medical residents approach their training and their profession.

The Housestaff Manual shares lessons from our clinical experiences on the medical services, including our annual review of the literature. Each year, this book reflects the diligent work of the residents, whose contributions join them with past generations of house officers.

We extend our gratitude to those residents who contributed their time and expertise to edit entire sections of this manual. Multiple sections have had significant updates and there are several new articles this year.

Cardiology: Will Pohlman & Sourik Beltran
Pulmonology & Critical Care: Sanjeethan Baksh & Joyce Zhou
Gastroenterology: Hanna Erickson & Eric Barash
Nephrology: Kyle Saysana
Infectious Disease: Christopher Radcliffe & Matthew Adan
Hematology & Oncology: Hatem Ellaithy & Catherine Gutierrez
Geriatrics & Palliative Care: Jade Connor
Endocrinology: Mirai Matsuura & Bryan Holtzman
Rheumatology, Allergy & Immunology: Marissa Savoie
Psychiatry: Richard Seeber
Primary Care: Unyime-Abasi Eyobio
Radiology: Rachel E. Grenier & Eric L. Tung
Procedures: Max Quinn

We would like to thank the many faculty, fellows, and administrators who assisted with this book. In addition, we are grateful to the residents in the ENT, General Surgery, Neurology, Ophthalmology, Radiology, and Urology programs who lent their expertise to the relevant sections.

Our work would not be possible without the countless hours of work by the previous editors of the MGH Department of Medicine Housestaff Manual. We hope we have lived up to their example.

1994	Albert Shaw & Ravi Thadhani
1995	Barry Kitch
1996	Sam Hahn
1998	Marc Sabatine
2000	Sherri-Ann Burnett & Bill Lester
2001	Jose Florez
2003	Andrew Yee
2004	Ishir Bhan
2005	Aaron Baggish & Yi-Bin Chen
2006	Bobby Yeh & Eugene Rhee
2007	Rajeev Malhotra
2008	Maha Farhat & W. Steve Sigler
2009	David Dudzinski & Elizabeth Guancial
2010	Roby Bhattacharya & Paul Cremer
2011	Kerry Massman & Vilas Patwardhan
2012	Michelle Long & Mihir Parikh
2013	Molly Paras & David Sallman
2014	Zaven Sargsyan & George Anesi
2015	Ang Li & Jehan Alladina
2016	Nino Mihatov & Tessa Steel
2017	Michael Abers & C. Charles Jain
2018	Kelsey Lau-Min & Jonathan Salik
2019	Melissa Lumish & Shilpa Sharma
2020	Jacqueline Henson & Alexandra Wick
2021	Leslie Chang & Daniel Gromer
2022	Mitu Bhattatiry & Sirus Jesudasen
2023	Hannah Abrams & Alexandra Doms

None of this would be possible without the support of the Department of Medicine. We extend special thanks to Gabby Mills, Libby Cunningham, Rachel Peabody, and Paula Prout. We also thank our Chief Residents – Blair Robinson, Sara Char, Josephine Fisher, and Darshali Vyas– as well as Jay Vyas, William Kormos, Joshua Metlay, and Jose Florez for their devotion to the housestaff and our education.

It has been an incredible honor to edit the Housestaff Manual. We look forward to the contributions of future generations of authors and editors in the years to come.

Elizabeth Gay, MD & Noemie Levy, MD
Department of Medicine, Massachusetts General Hospital
June 2024

As with any other medical reference, this manual is not intended to provide specific clinical care decisions in any individual case and should not substitute for clinical judgment. Please continue to consult your colleagues and supervisors, as well as the primary literature, whenever possible. We hope to provide guidance in the form of peer education and a forum for future experts to share their knowledge and hone their teaching craft for the benefit of their colleagues. We encourage you to use the manual, not only as a quick reference, but also as a teaching tool, a source of relevant publications, and a jumping-off point for personal exploration. Although we have reviewed every page, errors may exist. Please inform next year's editors here to ensure these errors are corrected.

MGH Housestaff Manual

Table of Contents

CARDIOLOGY
ACLS: Cardiac Arrest & TTM 1
ACLS: Bradycardia 3
ACLS: Tachycardia 4
ACLS: Defibrillation/Cardioversion/Pacing 5
EKG Interpretation 6
Narrow Complex Tachycardia 8
Wide Complex Tachycardia 9
Atrial Fibrillation & Flutter 10
QTc Prolongation 12
Chest Pain 13
Acute Coronary Syndrome 14
MI Complications 16
Cardiac Catheterization 18
Non-Invasive Cardiac Testing 19
Echocardiography 21
Inpatient Heart Failure 22
Right Ventricular Failure 25
Mechanical Circulatory Support 26
Pulmonary Artery Catheterization 27
Cardiac Devices: PPM, ICD, & CRT 28
Valvular Heart Disease 29
Pericardial Disease 31
Aortic Disease 32
Syncope 34
Severe Asymp. HTN & Emergency 35
Peripheral Artery Disease 36
Cardio-Oncology 37
Outpatient CV Health 38
Anti-Arrhythmic Medications 41
Telemetry and Physical Exam 42

PULMONARY & CRITICAL CARE
Respiratory Distress 43
Hypoxemia & Hypercapnia 44
Noninvasive Oxygenation/Ventilation 45
Interpretation of Chest Imaging 46
PFTs & Asthma 47
COPD 48
Bronchiectasis & Hemoptysis 49
Interstitial Lung Disease 50
VTE Diagnostics 51
VTE Management 52
Pulmonary Hypertension 53
Mechanical Ventilation 54
ARDS 56
ECMO 58
Sedation 59
Shock 61
Sepsis 62
Vasopressors 64
Toxicology 65

GASTROENTEROLOGY
Upper GI Bleeding 67
Lower GI Bleeding 68
Abdominal Pain 69
GERD & Peptic Ulcer Disease 70
Functional Dyspepsia 71
Nausea & Vomiting 72
Diarrhea 74
Constipation, IBS, & Colonic Disorders 75
Esophageal and Upper GI Disorders 77
Inflammatory Bowel Disease 78
Intestinal Disorders 80
Nutrition & Feeding 81
Pancreatitis and Pancreatic Mass 82
Weight and Weight Loss 83
Liver Chemistry Tests 84
Biliary Disease 85
Acute Liver Injury & Failure 86
Viral Hepatitis 87
Alcohol-Related Liver Disease 88
MASLD 89
End Stage Liver Disease 90
Hepatorenal Syndrome 94
Liver Transplant 95

NEPHROLOGY
Acute Kidney Injury 96
Glomerular Disease 98
Chronic Kidney Disease 99
Dialysis & Transplant 100
Advanced Diuresis 101
Acid-Base Disorders 102
Sodium Disorders 104
Potassium Disorders 105
Magnesium & Phosphorus Disorders 106
IV Fluids & Electrolyte Repletion 107
Urinalysis & Nephrolithiasis 108

INFECTIOUS DISEASE
Empiric Antibiotics & Antibiogram 109
Multidrug Resistant Organisms 112
Community Acquired Pneumonia 113
HAP/VAP & Aspiration Pneumonia 114
Viral Respiratory/Head & Neck Infections 115
Urinary Tract Infections 116
Skin & Soft Tissue Infections 117
Osteomyelitis 118
Bloodstream Infections & Endocarditis 119
Meningitis & Encephalitis 120
C. Difficile Infection 121
Invasive Fungal Infections 122
Tuberculosis 123
HIV/AIDS & Opportunistic Infections 124
Transplant ID 125
STIs & Travel Medicine 126
Tick-Borne Diseases 127
Mpox & Ectoparasites 128
Fever of Unknown Origin 129
Rare Diseases at MGH 130
Infection Control 131
Antimicrobial Dosing 132

HEMATOLOGY
Pancytopenia & Anemia 133
Sickle Cell Disease 135
Thrombocytopenia 136
Eosinophilia 137
Coagulation Disorders 138
Anticoagulation Agents 139
Anticoagulation Management 140
Transfusion Medicine 141
Transfusion Reactions 143
Peripheral Smear Interpretation 144

ONCOLOGY
Acute Leukemia 145
Lymphadenopathy & Lymphoma 147
Plasma Cell Disorders 148
MDS & MPN 149
Hematopoietic Cell Transplantation 150
CAR T-cell Therapy 153
Solid Organ Malignancies 154
Immune Checkpoint Inhibitors 156
Oncologic Emergencies 157
Febrile Neutropenia 158
Inpatient Leukemia & Lymphoma Regimens 159

GERIATRICS & PALLIATIVE CARE
Pain Management 161
Adv Care Planning & Code Status 163
End of Life & Pronouncement 165
Comfort Focused Care & Hospice 166
Geriatric Assessment & Frailty 167
Polypharmacy & Elder Abuse 168

RHEUMATOLOGY
Approach to Rheumatologic Disease 169
Arthritis 170
Connective Tissue Diseases 172
Vasculitis 173
Miscellaneous Rheumatologic Diseases 175
Autoantibodies 176
Rheumatologic Medications 177

ENDOCRINOLOGY
Outpatient Type 2 Diabetes Mellitus 178
Inpatient Diabetes Mellitus Management 180
DKA/HHS 181
Adrenal Insufficiency 182
Pituitary Disorders 183
Calcium Disorders 184
Osteoporosis & Vitamin D 185
Thyroid Disorders & Male Hypogonadism 186

ALLERGY & IMMUNOLOGY
Drug & Contrast Allergy 188
Angioedema & Anaphylaxis 190
Mast Cell Disorders 191
Primary Immunodeficiency 192

NEUROLOGY
Altered Mental Status 193
Dementia 194
Headache & Vertigo 195
Stroke & TIA 196
CNS Emergencies 198
Seizures 199
Weakness & Neuromuscular Disorders 200
Neuroprognostication 201

PSYCHIATRY
Consent & Capacity 202
Agitation 203
Delirium 204
Psychosis 205
Catatonia, NMS, & Serotonin Syndrome 206
Depression 207
Anxiety Disorders 208
Alcohol Use Disorder & Withdrawal 209
Opioid Use Disorder & Withdrawal 212
Other Substance Use & Drug Testing 213

PRIMARY CARE
Health Screening & Maintenance 215
Transgender Health 217
Women's Health 218
Men's Health 221
Sleep Medicine 222
HEENT Concerns 223
Nodules 225
Musculoskeletal Pain 226
Immigrant & Refugee Health 228
Climate Change & Health 229
Health Equity & Insurance 230
Disability Competent Care 231

CONSULTANTS
Calling Consults 232
Perioperative Medicine 233
Dermatology 235
Surgery 238
Urology 239
ENT 240
Ophthalmology 241
OB/GYN 242

RADIOLOGY
Radiology Basics 243
Contrast 244
Protocols 245
Interpretation of Common Studies 247

PROCEDURES
Ultrasound Basics 249
Ultrasound-Guided Peripheral IV 251
Central Line 252
Arterial Line 254
Intraosseous Line 255
Paracentesis 256
Lumbar Puncture 257
Thoracentesis 258
Pericardial Drain 259
Fluid Analysis 260
Tube Management 261
Exposures & Needle Sticks 264

LOGISTICS
Monitoring & Prophylaxis 265
Peri-Procedural Anticoagulation 266
Senior On Encounters 267
Post-Acute Care 268
Bias, Patient-Directed Discharge, ICE 269
MGH Directory 270

Cardiology

ACLS: Cardiac Arrest & TTM

UNRESPONSIVE PATIENT
Check circulation (pulse), airway and breathing (C-A-B)
No definite pulse within 10 sec.

→ **START CARDIOPULMONARY RESUSCITATION**
start compressions

Maternal Code Blue Algorithm: AHA 2020
AHA 2023 Guideline (Circ 2024;149:e254)
ILCOR 2023 Guidelines (Circ 2023;148:e187)

Call **CODE BLUE** (x6-3333, blue button on wall)
Call for defibrillator, backboard, ambu bag
Monitoring: tele, defib pads, cont O2, BP cuff

Compress 2-2.4" deep, 100-120BPM,
minimize interruptions & allow full recoil
Without ETT: 30:2 compressions to mask vent
With ETT: Δ compressors q2min, breaths q6-8s

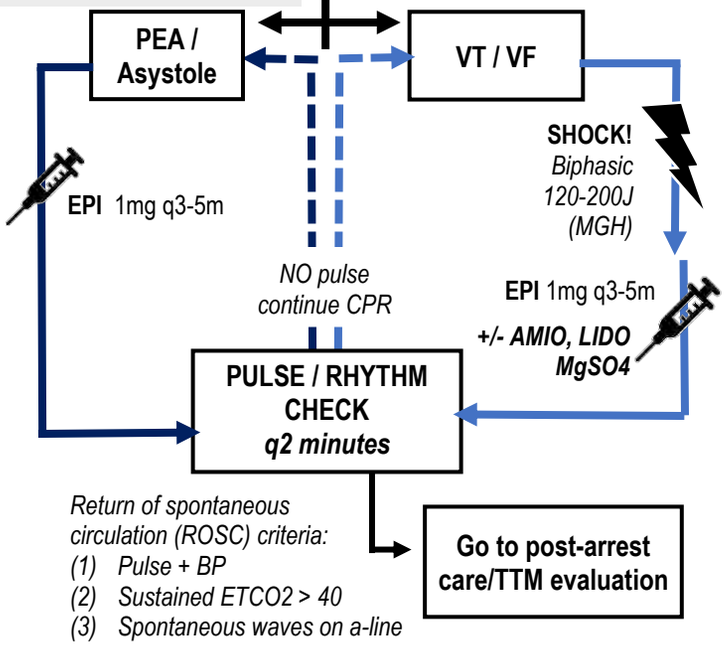
Rhythm check as soon as pads are on
Initial Defib if shockable, Epi if non-shockable

MGH CODE ROLES

- **Code leader**: Senior On
- **Code Whisperer**:
  AM = Consult SAR
  PM = Units NT
- **Pulse**: SDU JAR
- **Compressions**: Interns
- **Bring Lucas**: MICU Intern

CODE TASKS

- **A**ccess (IV>>IO), **A**irway
- **B**ackboard
- **C**ompression quality / **C**ode status (always confirm)
- **D**efibrillator, **D**rips
- **E**CMO/**E**mbolus **E**arly:
  - page <10min of coding
  - Consider Tenecteplase
- **F**amily (call HCP)



QUICK GUIDE: DOSING

- **DEFIB**: Biphasic (MGH) vs. Mono (360J), *if unknown, use max setting. repeat shocks @ same or ↑dose.* ***If no ROSC w/ 3 shocks consider AP pad placement and double sequential defib***
- **AMIODARONE**: 1st dose = 300 mg, 2nd dose = 150 mg
- **LIDOCAINE**: 1st dose: 1-1.5 mg/kg, 2nd dose: 0.5-0.75mg/kg
- **MGSO4**: if TdP 2g
- **HYPERKALEMIA**: 1g $CaCl_2$, bicarb 1-2 amp IV, D50W 1-2 amp, insulin 10u IV
- **NALOXONE**: minimum 2 mg IV if pulseless, if apneic but has pulse, 0.2-1 mg IV

Code Cart Medications

REVERSIBLE CAUSES (H&Ts)

- Hypovolemia
- Hemorrhage
- Hypoxia
- H+ ion (acidosis)
- Hypokalemia, hyperkalemia
- Hypothermia
- Thrombosis, coronary (ACS) & pulmonary (PE)
- Tension pneumothorax
- Tamponade (cardiac)
- Toxins (drugs, accidents)

MATERNAL CODE: ABCDEFGH

ACLS LOGISTICS & UPDATES

- **ACCESS**: try IV first, IO if necessary or IV not feasible; c/f reduced drug delivery esp with pre-tibial placement (AHA 2020 ACLS)
- **STAT LABS**: ABG with K & Hgb, CBC, BMP, LFTs, lactate, T&S, coags, fibrinogen, cardiac enzyme
- **MONITORING**: recommend wave capnography during CPR, keep ETCO2 at least >10mm H20, **ideally >20**
- **PROGNOSTICATION**: ETCO2 <10 mmHg in intubated pts after 20min CPR ~90% sensitive for no ROSC
- **PREGNANT WOMEN**: Apply left lateral uterine displacement, IVs above diaphragm, if receiving IV Mg, stop and give CaCl, resuscitative hysterotomy if no ROSC within 5min, TTM should still be considered with ROSC

Thrombolysis for Known/Suspected PE During Code

- **Tenecteplase (TNK - preferred over tPA in PE Code) Given as IV push over 5 seconds**
  - <60 kg: 30 mg
  - ≥60 to <70 kg: 35 mg
  - ≥70 to <80 kg: 40 mg
  - ≥80 to <90 kg: 45 mg
  - ≥90 kg: 50 mg
- If TNK is not available: Alteplase (tPA) 50mg IV over 2 minutes. Can give a second dose in 15min if no ROSC
- **Continue CPR for at least 15 minutes post lysis**
- **Contraindications (absolute):** prior ICH, ischemic stroke, head trauma (3mo), intracranial neoplasm or AVM, suspected aortic dissection, active bleeding
- **Heparin gtt after lysis when PTT falls to <2x normal**

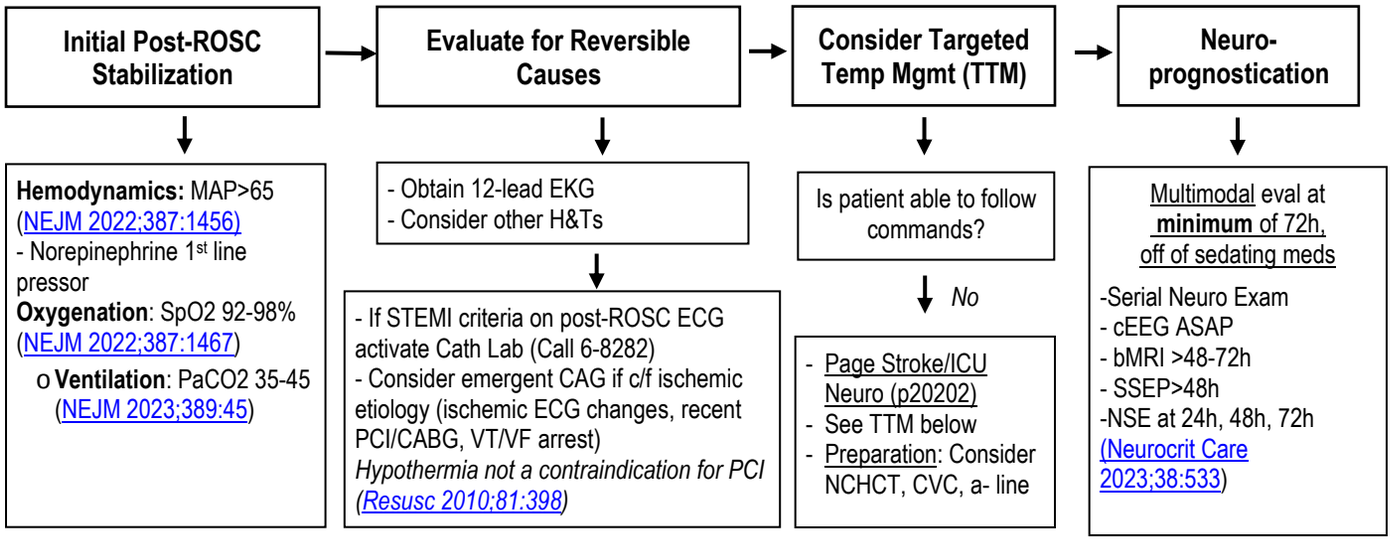
ECMO for Cardiac Arrest (ECLS, ECPR)

- STAT page "ECMO Consult MGH" or use "MGH STAT" app to call consult and for MGH ECMO guidelines **ideally <10 minutes from code initiation.**
- Indications: Age<75, no ROSC w/in 5 min, EtCO2 >10 mmHg
- Contraindications: BMI>45, EtCO2<10, lactate>18, pH<7.0, PaO2<50 on ABG, severe aortic regurgitation, aortic dissection, uncontrollable hemorrhage.
- Significant medical comorbidity should be discussed with ECMO team
- Favorable if initial shockable rhythm, shorter low-flow time
- Evidence: (Lancet 2020;396:1807; JAMA 2022;327:737, NEJM 2023; 388:299)
- See *ECMO*

Chris Schenck

Cardiology

ACLS: Cardiac Arrest & TTM


Initial Post-ROSC Stabilization
Evaluate for Reversible Causes
Consider Targeted Temp Mgmt (TTM)
Neuro-prognostication
Hemodynamics: MAP>65 (NEJM 2022;387:1456)
- Norepinephrine 1st line pressor
Oxygenation: SpO2 92-98% (NEJM 2022;387:1467)
o Ventilation: PaCO2 35-45 (NEJM 2023;389:45)
- Obtain 12-lead EKG
- Consider other H&Ts
- If STEMI criteria on post-ROSC ECG activate Cath Lab (Call 6-8282)
- Consider emergent CAG if c/f ischemic etiology (ischemic ECG changes, recent PCI/CABG, VT/VF arrest)
Hypothermia not a contraindication for PCI (Resusc 2010;81:398)
Is patient able to follow commands?
No
- Page Stroke/ICU Neuro (p20202)
- See TTM below
- Preparation: Consider NCHCT, CVC, a- line
Multimodal eval at minimum of 72h, off of sedating meds
-Serial Neuro Exam
- cEEG ASAP
- bMRI >48-72h
- SSEP>48h
-NSE at 24h, 48h, 72h
(Neurocrit Care 2023;38:533)

Targeted Temperature Management after Cardiac Arrest

Rationale: Fever is associated with worse neurological outcomes and neuronal damage due to inflammatory changes and biochemical cascades that develop following ischemia and reperfusion injury associated with cardiac arrest (Arch Intern Med 2001). **Goal is to avoid fever for neuroprotection and to be aggressive about diagnosing/treating infections.**

Causes of fever: Inflammatory response to global ischemia-reperfusion; Infection (high risk of aspiration/pneumonia, global ischemia -> gut ischemia -> bacterial translocation). Pan-culture and consider aggressive antibiotic treatment. Drug fever

***Importantly*: Per** MGH policy**, default strategy is maintenance of normothermia ≤37.5 C/≤99.5 F for at least 72 hours, w/central temperature monitoring (bladder preferred), and placement of temperature control device in all patients (eg Arctic Sun)**

TTM options if patient is not following commands (patient needs to be stable enough to wean sedation and paralysis for this exam)**:**

- **Normothermia** (≤37.5 C)
  - Allow passive rewarming until patient achieves T 37 C
  - Arctic Sun or other temperature control device to maintain T 37 C for 72 hr **Hypothermia** (33°C)
- **Mild Hypothermia** (T 33-36 C)
  - Individualized patient selection for mild hypothermia (T 33-36 C) decided by primary team
  - Temperature control device placed as soon as possible with goal of achieving target temp within 4h of ROSC
  - Maintain mild hypothermia for 24 hr, followed by normothermia for 48hr for total 72 hr
  - For pts treated with mild hypothermia, Re-warming should occur at a target rate of 0.25°C/h till normothermia achieved.
  - Monitor blood glucose/electrolytes closely
- Relative Contraindications to Mild Hypothermia: Recent head trauma, active bleeding, major surgery (<14d), refractory hypotension

Evidence:
- Targeted hypothermia (T 33 C) did not reduce 6-month mortality or survival with good neurologic outcome compared to targeted normothermia (T<37.5 C) (NEJM 2021;384:2283)
- Whether certain subgroups benefit from targeted hypothermia is uncertain (e.g., initial non-shockable rhythm (NEJM 2019;381:2327))

Sedation and Analgesia:
- Patients should undergo continuous sedation/analgesia if undergoing TTM w/mild hypothermia. Propofol is preferred sedative agent, dilaudid (or fentanyl) is preferred analgesic

Shivering:
- Stepwise approach to shivering in pts undergoing TTM (1st line: acetaminophen 650q6, Mg >3, 2nd line: skin counterwarming + dexmedetomidine OR propofol OR hydromorphone boluses, 3rd line: propofol + hydromorphone gtt, consider buspirone 30q8, 4th line: NMBA) (Neurocrit Care 2011;14:389)

Neuro-prognostication see Neurology section

Cardiology

ACLS: Bradycardia

Bradycardia with Pulse

HR<60 bpm and **symptomatic**

Circ 2020 Evidence Review | ACC/AHA Brady 2018

ASSESS PATIENT

- **Focused exam** → vitals, mental status, pupils, pulmonary edema, murmurs, warm/cold, other sx
- **Review** recent ECG, tele & labs, current meds, recent dose changes
- Obtain 12-Lead **ECG,** have **pacing pads** available
- **IV Access**: BMP, Mg, lactate ± trop
- **Monitor BP** freq., keep **O2** > 92%, maintain airway

IF PATIENT IS UNSTABLE:

☑ **Any of the following present?**

- **Hypotension**/shock
- **Altered mental status**
- **Ischemic chest discomfort**
- **Acute heart failure**/pulmonary edema

Trial medications, low threshold to pace

If pulseless arrest develops

→ ACLS PEA/Asystole

ATROPINE*

1mg bolus | q3-5mins (max 3g); 2hr half-life

do not give s/p heart transplant avoid with AV block Mobitz II or CHB

DOPAMINE IV infusion 5-20mcg/kg/min

OR

EPINEPHRINE IV infusion 2-10mcg/min

& ANTIDOTES BY CAUSE

TRANSCUTANEOUS PACING

- See pacing page for details
- Basics: Emergent 2mg lorazepam + 2mg dilaudid OR RICU for fentanyl/midazolam +/- intubate → turn to **PACER** → SET **RATE**: 100 BPM + SET **OUTPUT**: 100 mA → turn output down to minimum needed to capture → adjust rate down

TRANSVENOUS PACING WIRE

- Wire placed by cardiology
- Indications: 1) need for transcutaneous pacing despite meds, 2) unstable rhythm with **no quickly reversible** cause

IF PATIENT IS STABLE:

Monitor + Assess for reversible causes

- **Mobitz II & CHB with wide QRS** → always gets pacing wire even if stable, *call cards + ensure prepared to pace*
- *HOLD nodal blockers/anti-HTN if applicable*

ATROPINE & AV BLOCKS

Take-home message: Atropine will not help in the setting of CHB and Mobitz II

- Ineffective for blocks below AV node (↓response to atropine in pt with *AVB;* Resuscitation 1999;41:47)
- Potential worsening of Mobitz II 2/2 ↑HR (Am J Card 1974;33:333)

Bradycardia Diagnostic Algorithm

Are P waves present?

**=Wide QRS*
***Bold** = needs pacemaker*

No:
1. Sinus arrest w/ junctional escape OR ventricular escape [idioventricular]*
2. A fib/flutter w/ slow/variable conduction

Yes: Regular P-P interval?

No:
1. Sinus pause/sinus arrhythmia
2. Wandering pacemaker
3. Non-conducting PACs

Yes: Regular P-R interval?

No:
1. Mobitz I (# of P > # of QRS)
2. **CHB w/ junctional escape OR ventricular escape*** (P unrelated to QRS)

Yes:
1. Sinus bradycardia (# of P = # of QRS)
2. **Mobitz II** (# of P > # of QRS)

RHYTHM PEARLS

- If grouped beats → look for Mobitz I & II
- In 2nd degree AV block with 2:1 conduction, it is not possible to differentiate Mobitz I vs. Mobitz II
- Always remember to consider hyperkalemia!

ETIOLOGIES OF SINUS BRADYCARDIA AND/OR CHB

Italic = sinus brady, **Bold** = CHB

- ***Meds**, esp. in liver, renal dz*
- *SSS*
- ***Degenerative, calcific conduction dz***
- ***Elderly***
- *Hypoxia*
- ***Autoimmune/ Infectious CM***
- **s/p TAVR**
- ***Inc. vagal tone***
- *Elevated ICP*
- *Hypothermia*
- *Carotid dz + recent stent*
- ***Infiltrative dz***
- *Hypothyroidism*
- *Nocturnal/sleep apnea*
- *Athlete*
- ***Drugs/toxins***
- ***Ischemia/ACS*** (inferior MI, 2/2 *SA* vs **AV** nodal artery lesion)
- **Endocarditis**
- ***Lyme carditis, myocarditis***
- ***Pericarditis***
- ***Hyperkalemia***
- **s/p septal ablation**

SPECIFIC ANTIDOTES BY CAUSE

- **Beta blocker**: glucagon 3-10mg IV (if no response, repeat bolus, if response, infusion at 3-5mg/h)
- **Calcium channel blocker**: glucagon as above, calcium gluconate 3-6g q10-20min or gtt, insulin 1U/kg bolus with 0.5U/kg gtt
- **Digoxin**: dig immune FAB vial, 1 vial binds ~ 0.5mg digoxin, administer over 30min
- **Opioids**: naloxone 0.4-0.8mg IV, consider gtt
- **Organophosphate**: atropine 2-5mg IV (double dose q5min until effect), pralidoxime 1-2g IV over 15-30min

Cardiology

ACLS: Tachycardia

Tachycardia with Pulse

HR>120 bpm and **symptomatic**

ACLS Guidelines 2020

ASSESS PATIENT

- **Focused exam** → vitals, MS, pulmonary edema, murmurs, warm/cold, pupils, other sx
- Review: **most recent ECG**, tele, labs, meds, events
- Obtain: 12-Lead **ECG,** Defib + **pads**
- **IV Access**: BMP, Mg, lactate ± trop if c/f ischemia
- **Monitor BP** frequently
- **O2**: supplement to >94%, maintain airway

IS THE PATIENT UNSTABLE?

☑ **Any of the following present?**

- Hypotension / shock
- Altered mental status
- Ischemic chest discomfort / angina
- Acute heart failure / pulmonary edema

YES → *Analgesia (1-2mg dilaudid) + sedation (2mg lorazepam)*

If **narrow & regular**, can trial **adenosine**

NO → **MEDICATIONS** → **DETERMINE QRS WIDTH (> or <120 ms) & REGULARITY**

ACUTE DRUG DOSING

- **Adenosine**: **6mg rapid IV push** (followed by NS flush) + arm raise, can repeat x1 → 12mg if required, **central line = ½ peripheral dose,** relative contraindication in pts s/p heart transplant
- **Amiodarone**: **150mg IV over 10min** (may repeat x1); then infusion at 1mg/min x6h followed by 0.5mg/min x18h (max 2.2g/24h)
- **Diltiazem**: 0.25mg/kg IV bolus over 2min → gtt @ 5-10mg/h
- **Lidocaine**: **1.0-1.5mg/kg IV bolus** (usually 100mg), refractory → repeat 0.5-0.75mg/kg IV push q5-10min PRN, max 3mg/kg → maintenance infusion at 1-4mg/min; preferred agent if ↑QTc
- **Metoprolol: 2.5-5 mg over 2 min**; repeat q5 min; max dose 15mg
- **Procainamide**: **20-50mg/min or 100mg q5min** until any of the following: arrythmia terminates, ↓BP, QRS prolongs by 50% from baseline, or total 17mg/kg given → maintenance infusion at 1-4mg/min (adjusted for CrCl), avoid with ↑QTc
- **Sotalol**: **1-1.5mg/kg IV over 5 min**; then maintenance infusion at 10mg/min, contraindicated with ↑QTc & caution in pts w/ ↓EF

SYNCHRONIZED CARDIOVERSION VS. DEFIBRILLATION

Rhythm	Mode	Dose (J) *
Narrow & Regular	Sync	50-100
Narrow & Irregular	Sync	120-200
Wide & Regular	Sync	100
Wide & Irregular	**Defib**	120-200

**Biphasic (MGH)*

NARROW & REGULAR

Vagal Maneuvers → **Adenosine*** → IV BB or Dilt** Amio/Procainamide

**avoid post OHT*
***avoid if HFrEF*

DDx: ST, AT, orthodromic AVRT, AVNRT, Aflutter

If difficult to discern P waves, adenosine can slow rate to differentiate

NARROW & IRREGULAR

IV BB or Dilt* → *If persists* Amiodarone (*rhythm,rate*)** Digoxin (*rate*) *consider empiric 2g Mg*

**avoid if HFrEF*
***possible cardioversion, consider AC status*

DDx: AF + RVR, MAT, Aflutter/AT + variable block, ST + freq PACs

Consider chronicity/AC status prior to giving rhythm control for Afib/Aflutter

WIDE & REGULAR

Amiodarone *(OK for VT or SVT)* →

EF >40%: Lidocaine, Sotalol, Procainamide, Metoprolol
EF <40%: Lidocaine

Suspect SVT + conduction abnl → can trial vagal + adenosine *(will not worsen VT)*

DDx: monomorphic VT, SVT with aberrant conduction, antidromic AVRT, preexcitation, meds & electrolyte abnormality

WIDE & IRREGULAR

Lido + 2g Mg (over 15min) & treat myocardial ischemia

- ↑ *b/l QTc* → Torsades (TdP) 2-4g Mg & ↑HR (overdrive pacing, isoproterenol)
- *nml b/l QTc* → Non-TdP 2nd line = Amiodarone, procainamide

---

Pre-Excited SVT → **Procainamide** (nodal agents contraindicated)

DDx: PMVT (TdP & non-TdP), AFib/Aflutter/AT + pre-excitation vs aberrancy

Lido generally safe → effective for all PMVT and will not worsen pre-excited rhythms

VAGAL MANEUVERS:

- **Unilateral Carotid Massage:** supine with neck extended → steady pressure to carotid sinus (inferior to angle of the mandible at level of thyroid cartilage near carotid pulse), avoid if prior TIA/CVA in past 3mo, and those with carotid bruits; 5%-33% success
- **Modified Valsalva Maneuver:** semi-recumbent → blow forcefully into a 10cc syringe x10-15 seconds → reposition to supine and passively raise legs at 45° for 15 seconds; 43% effective in breaking SVTs vs 17% with standard Valsalva (Lancet 2015;386:1747)
- **Also consider:** cold ice face immersion or ice-water bag to face (diving reflex, more effective in children); 17% success.

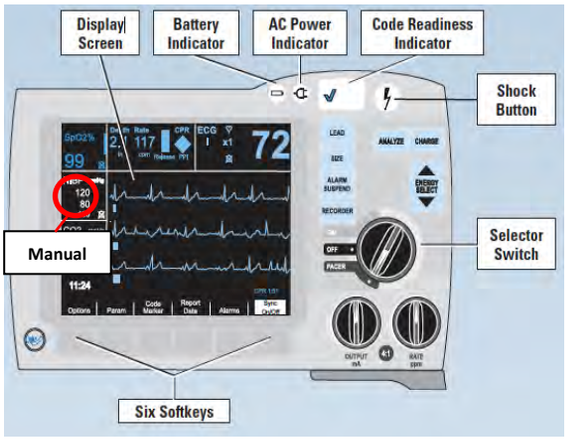
Cardiology ACLS: Defibrillation/Cardioversion/Pacing

External Defibrillation/Cardioversion/Transcutaneous Pacing

- **About the device**: the Zoll R Series is on all code carts & ICUs at MGH. This device allows for external defibrillation, cardioversion, and pacing with additional benefits (e.g. display ET-CO2, CPR quality feedback, & upload rhythm strips into Epic)
- **Additional supplies/resources**: Ambu bag, intubation equipment, RICU staff, backboard, suction
- **Medications**: use procedural sedation (typically 50mcg **fentanyl** → 2mg **midazolam**) when possible, requires **Cardiac Anesthesia/RICU**. In emergent situations, **Dilaudid** 1-2mg → **lorazepam** 2mg are reasonable alternatives (often readily available).

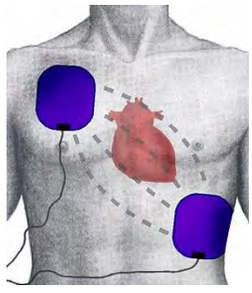
Display/Operation of Zoll R Series

- **Remove all clothing** covering the patient's chest. Dry chest if necessary. If the patient has excessive chest hair, shave it to ensure proper adhesion of the electrodes. Can rip off hair with extra set of pads if razor not readily available in acute situations.
- Attach hands-free therapy electrodes in anteroapical position (pictured) or anteroposterior position



Pearls:

- CPR ok to perform while pacing, take R-sided pulses (L not reliable)
- **Failure to capture?** Increase output, ensure pads are in correct location (avoid bony structures), consider ddx (barrel chest, COPD, hypoxia, tamponade/pericardial effusion, pneumothorax, acidosis, hyperK, obesity, MI, cardiac drug tox [dig, anti-arrhythmic])
- **Failure to sense?** Only happens with synchronous pacing – can switch to asynchronous pacing, reposition pads



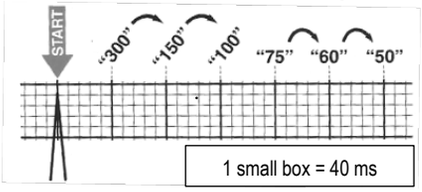
Defibrillation	Synchronized Cardioversion	Transcutaneous Pacing
Indications: pulseless VT or VF	***Indications: Unstable SVT or VT***	***Indications: Unstable bradycardia***
FIRST turn the Selector Switch to **ON.** Then press **Manual (**bottom left soft key) to change to ALS		
1. Default energy selection is 120 J. Initial dose 120-200 J. Use Energy Select (UP) & (DOWN) arrow keys to change the energy. 2. If there is a shockable rhythm on the pulse/rhythm check, press **Charge**. Continue CPR while charging. 3. Once charged, the **red shock button illuminates. Shout "Clear!**" then *press and hold* the illuminated **Shock** button at the top right of the console. 4. Resume CPR for 2 minutes before the next pulse/rhythm check	1. Select the desired energy using the up and down arrow keys on the front panel • Narrow, regular: **50-100 J** (atrial flutter often converts with 50 J) • Narrow, irregular: **120-200 J** (atrial fibrillation typically requires 150 J) • Wide, regular: **100 J** • Wide, irregular: **150-200 J** (defib dose) 2. Press the **Sync On/Off** button • Confirm that a **Sync marker** (🡻) appears on the monitor above each detected R-wave to indicate where discharge will occur • If necessary, use the **LEAD** and **SIZE** buttons to establish settings that yield the best display 3. Press the **CHARGE** button on the front panel. **Ensure patient is "clear"** 4. *Press and hold* the illuminated **SHOCK** button on the front panel. The defibrillator will discharge with the next detected R wave 5. If additional shocks are necessary, increase the energy level as needed • Confirm that a Sync marker (🡻) appears above each R-wave; you may need to press Sync between shocks 6. Anticoagulation required for at least four weeks after cardioversion	1. **PACER** appears as an option on the Selector Switch. Turn to **PACER** 2. Set the **PACER RATE (BPM)** to a value 20 bpm higher than the patient's intrinsic heart rate. If unknown or absent intrinsic rate, use 100 bpm • Observe the pacing stimulus marker on the display and verify that it is well-positioned in diastole 3. Increase **PACER OUTPUT (mA)** until the paced beats demonstrate **capture** ("threshold"); the output value is displayed on the screen. • Capture = widened QRS complex + loss of underlying intrinsic rhythm • Confirm mechanical capture with pulse check and/or by observing ventricular contraction w/ US 4. Set the **PACER OUTPUT** to the lowest setting that maintains consistent capture • Usually ~10% above threshold (typical threshold: ~40-80 mA) • Pressing and holding the 4:1 button temporarily withholds pacing stimuli, thereby allowing you to observe pt's underlying EKG rhythm & morphology • Treat underlying cause and/or pursue transvenous/permanent pacing

Cardiology

EKG Interpretation

Approach all EKGs systematically. Note rate, rhythm, QRS axis, intervals, complexes, chambers, ischemia/infarction. ***Compare with prior EKG.***

RATE (atrial, ventricular)



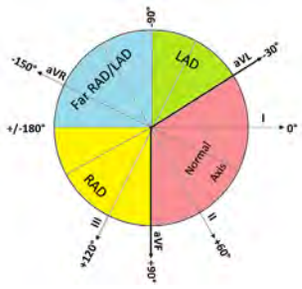
- If regular, 300 / #large boxes between each QRS (60,000/rate = R-R interval in ms)
- If irregular, count # of QRSs on EKG and multiply by 6 (printout = 10 sec)
- Normal 60-100bpm; <60 = bradycardia, >100 = tachycardia

RHYTHM (regular or irregular; sinus vs non-sinus)

- **Sinus rhythm** = P before every QRS and QRS following every P, regular w/ rate 60-100, normal P wave axis
- P waves/morphology: determine 1) if **P wave** is present (best leads to visualize P wave are II and V1), 2) **atrial rate** (100-180: sinus tachycardia; 140-220: atrial tachycardia, AVNRT, AVRT; 260-320: atrial flutter), and 3) **axis** (Normal axis: P wave upright in I/II, biphasic in V1)
- QRS morphology: narrow (<120 ms) = supraventricular origin; wide (>120 ms) = aberrant supraventricular conduction or ventricular origin
- P wave/QRS complex association: if not 1:1, determine if number of P>QRS (AV block) or P<QRS (AV node, His-Purkinje, or ventricular rhythm). If P precedes QRS, evaluate **PR interval**. If P after QRS, evaluate **RP interval**. Determine if PR or RP interval is fixed or variable
  - **AVB**: first degree (PR >200ms); second degree Mobitz I/Wenckebach (PR progressively longer until dropped QRS); second degree Mobitz type II (sudden dropped QRS without PR lengthening); third degree (dissociation of P and QRS)

QRS AXIS (use direction of QRS complex)

Axis Deviation	Lead I	Lead II	Lead aVF	Differential Diagnosis
Normal (-30 to +90°)	⊕	⊕	⊕/-	
Leftward (-30 to -90°)	⊕	-	-	Normal variant, mechanical shifts, LVH, LBBB, LAFB, congenital heart disease, emphysema, hyperK, ventricular ectopic rhythms, WPW, inferior MI, pacing
Rightward (+90 to +180°)	-	⊕	⊕	Normal variant, mechanical shifts, RV strain, RVH, LPFB, dextrocardia, ventricular ectopic rhythms, WPW, lateral MI (RBBB rarely causes RAD)
Extreme/Northwest (180 to -90°)	-	-	-	Lead transposition, ventricular ectopic rhythms, hyperK, artificial pacing, severe RVH



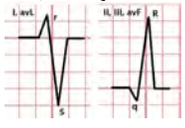
- Clockwise/counterclockwise rotation ("R wave progression"): R wave amplitude typically increases from V1 to V5, amplitude of R becomes greater than S at V3 or V4. Early or late R wave progression is nonspecific and can be normal (Am Heart J 2004;148:80)
  - CCW ("early R wave progression"): R>S prior to V3. Causes: RVH, WPW, LAFB, posterior MI.
  - CW ("late R wave progression"): R>S after V4. Causes: cardiomyopathy, LVH, LBBB, anterior MI.
- **Low voltage**: average QRS amplitude <5 mm in I, II, III *and* <10 mm in precordial leads
  - DDx: obesity, pericardial effusion, PTX, COPD, PE, restrictive or infiltrative CM (particularly amyloidosis), severe hypothyroidism, or anasarca

COMPLEXES AND INTERVALS (Circ 2009;119:e241)

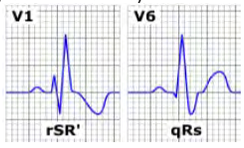
- P wave: right and left atrial depolarization. Normal: duration <120ms, voltage ≥ 0.1mV in I, area (1/2 duration x voltage in II) ≤ 4 (Circ Arrhythm Electrophysiol. 2022; e010435)
- PR interval: atrial depolarization, AV node and His-Purkinje conduction. Normally 140-200ms, changes with rate (shortened at faster rates, longer at lower rates) d/t autonomic effects on AV nodal conduction
- QRS: ventricular depolarization. Normal duration 60-110ms, not influenced by HR. QRS 100-120ms = incomplete BBB or intraventricular conduction delay (IVCD). QRS >120ms = BBB, ventricular activation (PVC, VT, fusion beats, WPW, paced beats), hyperK, Na channel poisoning, aberrancy, hypothermia.

LAFB: left axis deviation, QRS <120, qR in I, aVL and rS in II, III, aVF. Common, nonspecific.

LPFB: right axis deviation, QRS <120, rS in I, aVL and qR in II, III, aVF. Rare in isolation, usually w/ RBBB.

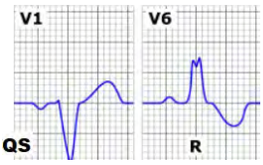


RBBB: QRS >120, rSR' in V1 or V2, wide qRS in V6, S>R duration in I, V6. Causes: infection (myocarditis), infarction, increased RV pressure (PE, Cor Pulmonale).



Bifascicular: RBBB + LAFB or LPFB

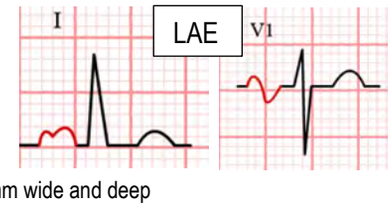
LBBB: QRS >120, wide negative QS in V1, wide tall R in I, aVL, V5, V6. Causes: primarily dilated cardiomyopathy (ischemia, infection, valvular, infiltrative).

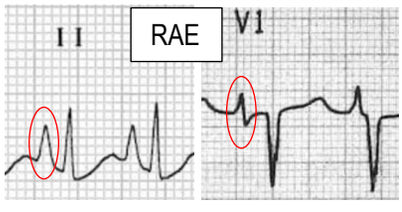


- ST segment: normally isoelectic plateau of ventricular potentials
- T wave: ventricular repolarization, with a slow upstroke and a rapid return to the isoelectric line after peaking. Usually asymmetric and in the same direction as the QRS. Should have smooth contours (bumps in T are usually buried P waves)
- U wave: occurs in the same direction as the T wave, rate-dependent (shorter at faster rates); DDx: bradycardia, hypoK/Mg/Ca, hypothermia
- QT interval: ventricular depolarization and repolarization. Excludes U wave unless fused with T wave. Rate-dependent (shortened at faster rates). Normal <440ms (M) and <460ms (F). Reassuring if QT is less than half R-R interval with normal HR

CHAMBER ENLARGEMENT (Circ 2009;119:e251) *all have low Sn and Sp*

- LVH: Sokolow-Lyon criteria: S in V1 + R in V5 or V6 ≥35mm *OR* R in aVL ≥11mm. Cornell criteria: S in V3 + R in aVL >28mm (M) or >20mm (F). For non-voltage based criteria consider Romhilt-Estes score
- RVH: R>S or R ≥7mm in V1, S ≥7mm in V5 or V6
- LAE: P wave duration ≥120ms (>2.5mm), widely notched P (≥40ms), negative component of P in V1 >1mm wide and deep
- RAE: P wave height >2.5mm in II ("P-pulmonae"), initial positive P wave in V1/V2 ≥1.5mm





Brian Huang

Cardiology EKG Interpretation

ST Segment and T wave changes (JACC 2009;53:1003)

- Analyze abnormalities along the vectors of ventricular depolarization and repolarization (QRS-ST-T)
- **T wave abnormalities**: hyperacute, symmetric T waves can be found within minutes of ischemia, followed by T wave inversions (≥1mm in 2 contiguous leads). TWI normal if only in aVR, V1 or III. Isolated TWI in aVL may indicate mid-LAD lesion vs inferior MI (J Emerg Med 2014;46:165)
  - TWI DDx: myocardial ischemia (symmetric), prior MI, acute PE (RV strain pattern: TWI V1-V4, II, III, aVF, RBBB, ↑Sp/↓Sn: S1Q3T3, TWI III+V1 high PPV for PE > ACS (Am J Card 2007;99:817)), apical HCM (TWI V1-V6), arrhythmogenic right ventricular cardiomyopathy (TWI V1-3), intracranial pathology ("cerebral T waves", asymmetric), myocarditis, pericarditis, BBB pattern, V-paced, LVH with "strain", normal variant, digoxin effect (biphasic w/ initial neg. predominance), Type 1 Brugada (TWI V1-V2), athlete's heart. (World J Cardiol. 2015; 7(2): 86-100).
  - De Winter's T waves: 2% of STEMIs present with tall, symmetric T waves + >1mm STD at J point in precordial leads + 0.5-1mm STE in aVR c/w acute LAD occlusion (NEJM 2008;359:2071)
- **ST depression**: suggests subendocardial injury, ≥0.5mm below the baseline (PR segment), measured 80ms after the J point in 2 contiguous leads
  - Downsloping or horizontal = more ominous. STD do not localize to territories (Circ Res 1998;82:957)
  - Always look for STE to rule out reciprocal STD. STD in V1-V3 can be posterior MI (check posterior leads)
- **ST elevation**: suggests transmural ischemia, ≥1mm in leads except for leads V2-V3 (≥2mm in M ≥40y, ≥2.5mm in M ≤40y, ≥1.5mm in F), use PR segment (isoelectric interval), measured at the J point (Circ 2018: e618-e651). **Differential diagnosis**:

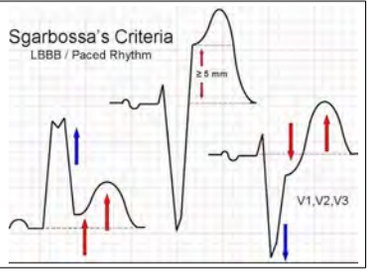
Diagnosis w/ STE	Characteristic ECG Findings (NEJM 2003;349:2128; Annals 2004;141:858; NEJM 2004;351:2195)
Acute STEMI	STE in ≥2 contiguous leads in coronary distribution (see table), reciprocal STD
LVH	Concave STE in V1-V3 with STD and TWI in I, aVL, V5-V6, voltage criteria as above
LBBB	Concave STE in V1-V3, discordant with negative QRS
Acute pericarditis	Diffuse STE (usually <5mm), PR depression, amplitude of STE:T wave (in mm) >0.26 is specific
Printzmetal's angina/vasospasm	Transient STE in coronary distribution as in STEMI
Acute PE	STE in inferior and anteroseptal leads, mimics acute MI, complete or incomplete RBBB
Stress-induced cardiomyopathy (Takotsubo's)	Diffuse STE in precordial leads w/o reciprocal inferior STD, STE followed by deep TWI
Ventricular aneurysm	Persistent STE after MI, often with abnormal Q waves
Early repolarization	J point elevation ≥1mm in 2 contiguous leads (esp V4), amplitude of STE:T wave (in mm) <0.25
Brugada syndrome	rSR' and downsloping STE in V1-V2 (see below)
Male pattern	1-3mm concave STE, often highest in V2
Normal variant	STE in V3-V5, TWI, short QT, high QRS voltage
Cardioversion	Marked (often >10mm) and transient following DCCV

Coronary Distribution

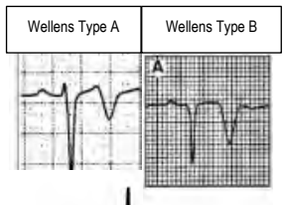
EKG Lead	Territory	Coronary Vessel
V1-V2	Anteroseptal	Proximal-mid LAD
V5-V6	Apical	Distal LAD, Distal LCx, RCA
I, aVL	Lateral	LCx (proximal)
II, III, aVF	Inferior	RCA (85%), LCx
V7-V9	Posterior	LCx > RCA
V4R	RV	RCA, LCx
aVR		L main or 3vD

Modified Sgarbossa Criteria:
To diagnose acute MI w/ LBBB (does not apply to pacers). Below = traditional version (need 3pts)

- Concordant STE >1mm in any lead = 5 points
- Discordant STE >5mm in any lead = 2 points
- STD >1mm in V1-V3 = 3 points

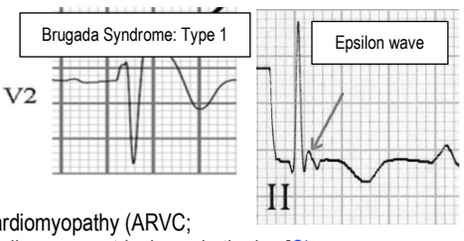


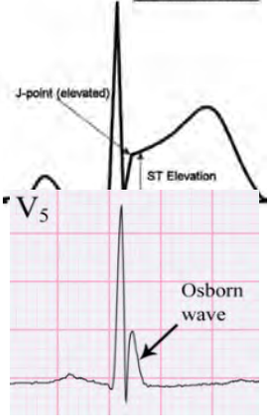
- **Q wave**: usually a marker of scar, pathologic Q waves must be deep (>1mm), 25% height of QRS, and 40ms long. More likely 2/2 prior MI if inverted T wave in same lead. Small "septal" Q physiologic in V5, V6, I, aVL
- **Wellens Syndrome**: sign of **critical proximal LM or LAD lesion**, 75% MI in <2w. Often pain free with h/o angina. Normal/slightly elevated troponin. Type A: 25% biphasic (up then downsloping morphology) T waves in V2 and V3. Type B: 75% symmetric, deeply inverted precordial T waves. Isoelectric or minimally elevated (<1mm) ST segment. No precordial Q waves (Am J Emerg Med 2002;20:7; Am Heart J 1982;103:730)



Other

- **J-Point Elevation Syndromes**: J point is when QRS transitions to ST segment.
  - Early repolarization pattern: benign STE in absence of chest pain, terminal QRS slur, or terminal QRS notch
    - Suspicious features: FH sudden cardiac arrest or early unexplained death, workup c/f channelopathy, h/o unheralded syncope suggestive of arrhythmogenic pathogenesis (Circ 2016;133:1520)
  - Brugada Pattern: Syndrome only if symptomatic. Autosomal dominant SCN5A loss of function in 10-30%, M>F, common to have nocturnal cardiac arrest, p/w VT/VF or sudden cardiac death (Circ Arrhythm Electrophys 2012;5:606)
  - Osborn wave: hypothermia T<93ºF, elevation of J point height ~ proportional to degree of hypothermia in II, V2-6. More dome-shaped than Epsilon wave.
  - Epsilon wave: found in arrhythmogenic right ventricular cardiomyopathy (ARVC; inherited, age 10-50, fibro-fatty replacement of RV myocardium → ventricular arrhythmias [Circ 2005;112:3823]), most Sp in V1 (30% with ARVC), low frequency, positive terminal deflection in V1-V3.





- **Electrolyte Abnormalities**

Abnormality	Characteristic ECG Findings
Hypokalemia	Prolonged QT, ST depression, flattened T wave, prominent U wave, higher amplitude P wave, prolonged PR
Hyperkalemia	Peaked, *symmetric* T wave → flat P → prolonged PR ± AVB → widened QRS ± BBB (severe) → sinusoidal
Hypocalcemia	Prolonged QT, unchanged T wave
Hypercalcemia	Shortened QT (if severe, T-wave can merge with QRS and mimic STE)

Cardiology

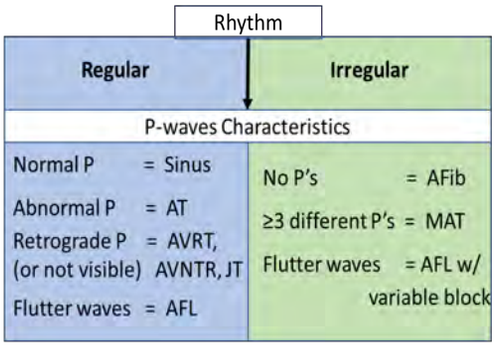
Narrow Complex Tachycardia

Narrow Complex Tachycardia (QRS <120ms)

(NEJM 2012;367:1438; Mayo Clin Proc 1995;70:371)

Diagnostic approach & general principles:

1. **Determine the width of the QRS complex**
2. **Determine if the rhythm is regular or irregular**
3. **Assess for the presence of P waves (noting location, axis and morphology)**
4. **Compare to baseline ECG**
5. Treatment (See *ACLS: Tachycardia* and *Atrial Fibrillation/Flutter*)
   - If unstable → synchronized cardioversion
   - If stable → vagal maneuvers (carotid massage/valsalva/ice water on face). Adenosine can resolve diagnostic dilemmas and treat AVNRT and AVRT (adenosine is blocked by theophylline/caffeine & potentiated by dipyridamole)
   - Acute treatment for all others is BB, CCB or amiodarone (use caution with pharmacologic cardioversion and consider ruling out intra-atrial clot if pt has been in Afib/flutter for > 48 hours and has not been anticoagulated for 3 weeks prior to cardioversion)



Regular, narrow complex tachycardias

Sinus Tachycardia (rate >100, maximum HR = 220-age)
Gradual onset
Most important to determine **underlying cause**: hypovolemia, hemorrhage, withdrawal (EtOH, BZD, opiate, BB), intoxication, fever/infection, pain, hypoxemia, PE, anemia, tamponade, dissection, endo (hyperthyroidism, adrenal insufficiency, pheo)

Focal Atrial Tachycardia (AT) (atrial rate 100-200)
Due to abnormal automaticity at a single atrial focus other than the SA node, or due to a reentrant circuit within the atria
Discrete P waves present, but of abnormal morphology +/- axis (i.e. p wave inverted in inferior leads)
Classic digoxin toxicity is AT w/ variable AVB
Usually seen in otherwise normal hearts

Junctional Tachycardia
Due to increased automaticity within the AV node (or reentrant rhythms, e.g., AVNRT)
P waves may be absent (e.g. buried within the QRS complex), inverted and/or retrograde

Atrioventricular Nodal Re-entrant Tachycardia (AVNRT) (rate 150-250)
Arises from functional re-entry within AV node
P wave, if visible, is retrograde (may be seen as a pseudo R-wave in lead V1, or pseudo S wave in lead II) – note that retrograde P waves appear earlier in AVNRT than in AVRT
Short RP (when conducting fast-slow), however more commonly no RP (when conducting slow-fast)
Trigger PAC (slow-fast) > PVC (fast-slow)
Young adults, F>M, usually arises within structurally normal hearts

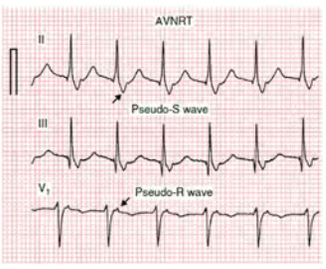
Orthodromic Atrioventricular Re-entrant Tachycardia (AVRT) (rate usually 150-250)
Ventricular depolarization occurs via the AV node, however an accessory tract allows for retrograde conduction to the atria (if ventricular depolarization occurs via the accessory tract, the resultant QRS is wide and is termed "Antidromic, see "WCT")
Retrograde P waves may be present (if so, they appear later than those seen in AVNRT)

Irregular, narrow complex tachycardias

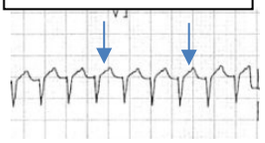
Multifocal Atrial Tachycardia (MAT) (rate ~100-150)
Discrete P waves present, of ≥3 morphologies
Irregular due to varying PP, PR, and RR intervals
Seen in COPD, pHTN, CAD, electrolyte disarray, aminophylline/theophylline use

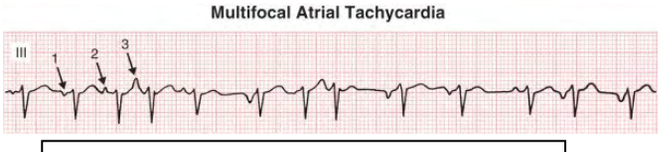
Atrial Fibrillation (AF)
No coordinated atrial activity (P wave absent), irregular, fibrillatory waves present
Arises from numerous re-entrant tracts in atria or pulmonary veins
If associated with pre-excitation, the result is an irregular, WCT

Atrial Flutter (AFL) (P wave rate 250-300)
Arises from true (isthmus-dependent, typical) or functional (isthmus-independent, atypical) re-entry in R atrium
May be regular (e.g. 2:1, 3:1, 4.1, etc.) or irregular (if variable AV block)
Counterclockwise: negative flutter waves in II, III, aVF
Clockwise: positive flutter waves in II, III, aVF
No isoelectric baseline, atrial rate ~300 (always >250) usually with 2:1 conduction but can have variable conduction

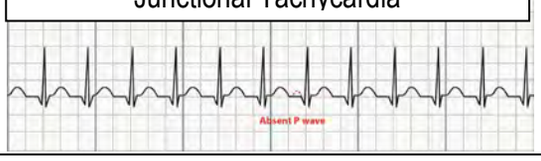


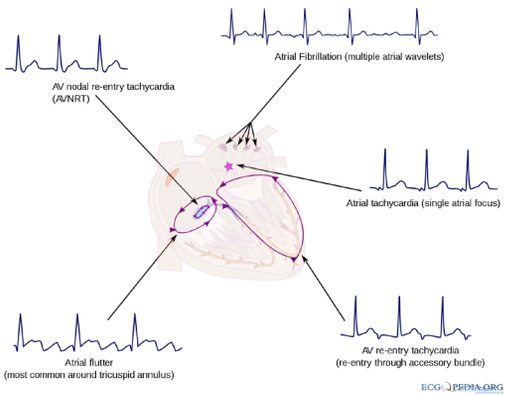
AVRT
Note: blue arrows = retrograde P waves





Junctional Tachycardia




Atrial Fibrillation (multiple atrial wavelets)
AV nodal re-entry tachycardia (AVNRT)
Atrial tachycardia (single atrial focus)
Atrial flutter (most common around tricuspid annulus)
AV re-entry tachycardia (re-entry through accessory bundle)
ECG PEDIA.ORG

Cardiology

Wide Complex Tachycardia

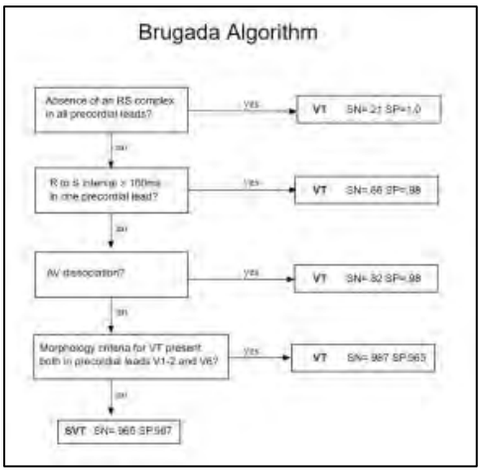
Wide Complex Tachycardia (QRS ≥120ms)

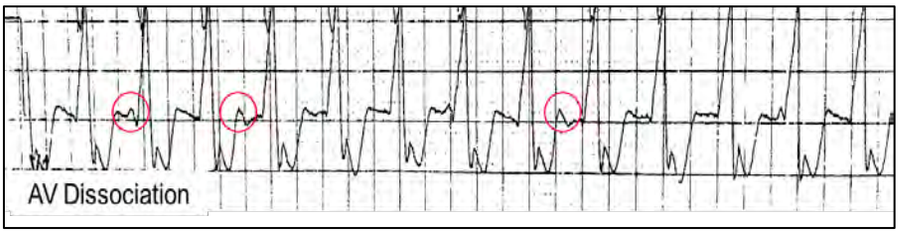
DDx = VT (80%), **SVT with aberrant conduction**, **pre-excitation syndrome**, or pacemaker-mediated tachycardia

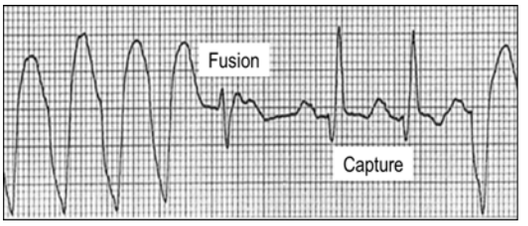
Features that Favor VT (note: absence does NOT rule out VT)	**Features that Favor SVT with Aberrancy**
• **Very wide QRS** (>160 ms), **Rate > 120** (if <120, consider Na channel toxicity or VT in someone already on significant antiarrhythmics) • **New northwest (aka extreme)** axis (leads I and II negative) • **AV dissociation** (often V rate > A rate): *pathognomonic for VT* • **Concordance**: all QRS in V1-6 are completely (+) or completely (-) • Partial (**fusion beat**) or complete (**capture beat**) depolarization of His-Purkinje by a competing supraventricular (atrial / junctional) rhythm • **Basel algorithm** = VT likely if ≥2 of 3 present: (1) high risk substrate (prior MI, EF<35, prior VT/has ICD), (2) lead II time to first peak >40ms (1 small box), (3) aVR time to first peak >40ms (1 small box). ▪ Very effective: 93% sensitive & 90% specific [similar to other algorithms] but faster diagnosis [36s vs 105s with Brugada] (JACC 2022;7:831).	• **Known BBB:** ventricular conduction delay (RBBB, LBBB, IVCD) with similar morphology and axis as seen on prior / baseline ECG • **Evidence of His conduction**: QRS has sharp initial deflection (suggests initial use of His-Purkinje system followed by aberrancy) • **Pre-excitation** on baseline ECG → supports antidromic AVRT or pre-excited atrial fibrillation • **R wave peak time < 40msec** (measured in lead II and aVR)

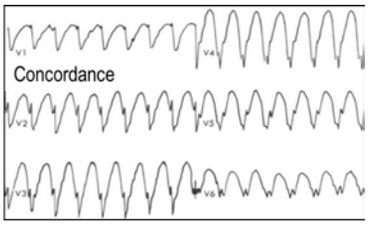
Other important considerations:

- Hyperkalemia, antiarrhythmic drugs (digoxin, class IA or IC, amiodarone), TCA overdose
- Pacemaker-mediated/endless loop tachycardia: retrograde VA conduction of V-paced beat misidentified as native A-beat → V-pacing. ECG shows V pacing at upper rate limit
- Sensor induced tachycardia: inappropriate sensing of nonphysiologic stimuli (vibrations, electrocautery, etc.) and pacing.







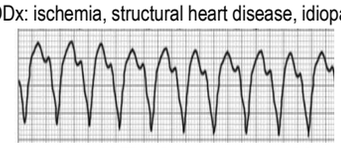


Management of VT (also see *ACLS*: *Tachycardia*)

- Often no way to confidently distinguish VT or SVT with aberrancy. If there is any doubt, treat like VT
- **Consider underlying processes**: active ischemia, CAD with scar, electrolyte derangement (low K, low Mg), indwelling lines
- Check and replete electrolytes **(K>4, Mg>2)**
- Review baseline ECG for evidence of long QT or pre-excitation

Monomorphic VT

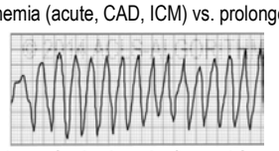
DDx: ischemia, structural heart disease, idiopathic



1. **Non-sustained VT** (>3 complexes, <30 secs)
Asymptomatic → monitor, treat underlying cardiac comorbidities (e.g., CAD, HF)
Symptomatic → nodal blockade (BB>CCB), then AADs
2. **Stable and sustained** (>30 seconds) → antiarrhythmic agent (e.g. amiodarone, lidocaine, procainamide [WPW])
3. **Unstable** → synchronized cardioversion (100J) if pulse; defibrillation if pulseless

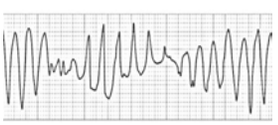
Polymorphic VT

DDx: ischemia (acute, CAD, ICM) vs. prolonged QTc



1. Evaluate for **ischemia** & need for revascularization
2. **Stable** → magnesium 2-4g over 10-15min, ↑HR (isoproterenol, overdrive pacing), ↓QTc (**lido**), avoid bradycardia (amio, CCB/BB)
3. **Unstable** → defibrillation

Torsades de Pointes



Polymorphic VT that occurs with underlying prolonged QTc (congenital or acquired). Can be prompted by PVC falling on T wave of previous beat (R on T phenomenon)
Note: isoproterenol = pure chronotrope will reduce RoT

VT Storm: ≥3 sustained episodes of unstable VT within 24 hours

- **Lido bolus** (preferred if prolonged QTc), **Amio bolus** (careful if long QT), co-admin propranolol 60mg q6 [JACC 2018;71:1897]
- **Anti-tachycardia pacing** (ATP): overdrive pacing at a faster rate than VT
- Treat / minimize ischemia: **revascularization**, **IABP** to improve coronary perfusion, reduce preload / afterload
- Reduce autonomic tone: **intubation** and **sedation**, stellate ganglion block/cardiac sympathetic denervation
- Call EP +/- MCS/Shock Team
- **Catheter ablation (**VANISH trial, NEJM 2016;375:111)

Cardiology

Atrial Fibrillation & Flutter

ATRIAL FIBRILLATION

Epidemiology (Heart Rhythm 2012;9:632)

- RF: age, obesity, HTN, smoking, EtOH, DM, previous MI, HF, OSA
- Recurs in majority of cases due to secondary precipitant (surgery, infection, MI, thyrotoxicosis, acute alcohol, PE)
- Often co-exists with atrial flutter (Circ Arrythmia EP 2009;2:393)
- Racial, ethnic, and gender inqeuities persist in AF screening and management (Circ 2024; 149: e1-e156)

New AF Classification (Circ 2024; 149: e1-e156)	
Stage I: At-risk for AF	Presence of modifiable and non-modifiable RFs
Stage II: Pre-AF	Structural or electrical findings that predispose to AF (atrial enlargement or ectopy etc.)
Stage III: AF Spectrum	Spectrum including paroxysmal (3A, <7d), persistent (3B, >7d), long-standing persistent (3C, >12mo), or s/p successful AF ablation (3D)
Stage IV: Permanent AF	Decision is made to no longer pursue rhythm control

Clinical Evaluation of New-Onset AF

- H&P: **presence & timing of sx**, HTN, DM, valve dz, HF, angina, congenital heart disease, OSA, FH of AF, acute precipitants (e.g. EtOH, thyrotoxicosis, sympathomimetic drugs, surgery, MI, myocarditis, PE, acute pulmonary disease, infection)
- ECG: absence of discernible p waves, irregularly irregular R-R intervals (if regularized, may represent escape rhythm and CHB)
- TTE: LV function, enlarged LA/RA size, valve function, pulmonary HTN, LA thrombus (better visualized with TEE)
- CXR: evaluate for pulmonary parenchymal processes, pulmonary vasculature/edema
- Labs: TFTs, LFTs, BUN/Cr, CBC, NT-proBNP, BMP (K,Mg)
- May also need longer term rhythm monitoring (Holter, Zio patch). Consider stress test if signs/sx of ischemic heart disease.
- Smartwatch notification has PPV 0.84 for AF on subsequent simultaneous EKG in patients > 65 (NEJM 2019; 381:1909-1917)

Acute Management of AF with Rapid Ventricular Response

Hemodynamically stable?

Stable (SBP >90)

Rate control (IV if HR >130 or sx, follow with PO agent once rates controlled)
- **Magnesium:** 2-4 g empiric IV Mg + nodal agents ↑ success of rate and rhythm control (JACC 2021; 78:375-381)
- **Beta blocker**: metoprolol preferred in most cases
  - IV: bolus 2.5-5mg over 2min, repeat prn q5min, max dose 15mg
  - PO: fractionated, up to 400mg total daily dose
  - Caution if severe bronchospasm and w/ rapid escalation in pts w/ ADHF
- **Calcium channel blocker**: diltiazem
  - IV: bolus 0.25mg/kg (average dose 10-25 mg) over 2min, repeat prn q10-15min
  - PO: fractionated, up to 360 mg total daily dose
  - Reduce dose with hepatic or renal impairment
  - Avoid in pts with LVEF<40% and in ADHF

Peri-stable (SBP 80-90)

If borderline BP, carefully attempt **low dose** BB or CCB (can try concomitant **IVF** if pulm edema not a concern)

Consider BP-sparing agents: (weigh risk of pharmacologic cardioversion if not on AC)
- **Amiodarone**: 150mg IV over 10 min, can repeat x1 if needed and start gtt at 1mg/min
- **Digoxin**: 0.5mg IV followed by 0.25mg IV q6h x2, total load 1mg. Check level s/p load. Careful in renal impairment, contraindicated if accessory pathways

Unstable (SBP<80)

Usually HR >150, signs of shock (AMS, cool ext.), refractory pulmonary edema or angina

Synchronized cardioversion: start with 150J (Biphasic)

If pressors needed: **phenylephrine** is first-line given reflex bradycardia

Higher HRs (>140) more likely to cause HoTN alone; lower HRs may cause HoTN if systolic or diastolic dysfxn, or decreased preload ("loss of atrial kick")

Correct **underlying etiology** whenever possible once stable (e.g. infection, volume, PE, EtOH, PTX, PNA, MI, pericarditis)

Cardioversion (ALWAYS consider high risk of embolic stroke if any interruptions in AC for 3 weeks prior)

- **Indications**: Urgent: ischemia, end-organ hypoperfusion, symptomatic hypotension, severe pulmonary edema; Elective: new-onset AF or unacceptable symptoms from persistent AF
- **Synchronized Electrical Cardioversion** (DCCV): start with 150J (biphasic),↑energy if NSR not achieved. See *ACLS: Cardioversion*.
- **Chemical Cardioversion**: success rate significantly higher for acute (<7d) compared with longer duration AF
  - Pill-in-pocket (flecainide, propafenone) + BB or CCB
  - Ibutilide (most effective) or Dofetilide or Procainamide
  - Amiodarone (IV infusion weakly effective for cardioversion, PO load over 3-4w, 27% rate of cardioversion)
- **Anticoagulation** (applies to BOTH chemical and electrical)
  - Pre-cardioversion: if definitive new onset **<48h**: may proceed without anticoagulation. If Afib onset **>48h or unclear**: anticoagulate for 3w prior to cardioversion *or* obtain **TEE** immediately prior to cardioversion (NEJM 2001;344:1411)
  - Post-cardioversion: anticoagulate for at least **4 weeks after cardioversion** (risk of myocardial stunning and AF recurrence, but unproven efficacy). Anticoagulation beyond 4 weeks after reversion to NSR is based on CHA_2DS_2-VASc and HAS-BLED scores

Risk Assessment (Risk scores DON'T account for the complete spectrum of RFs - Individualize AF management)

- **CHA_2DS_2-VASc**: 1pt for **C**HF, **H**TN, **A**ge 65-74, **D**M, female **S**ex, **V**ascular disease; 2pt for **A**ge≥75, **S**troke/TIA. CHA_2DS_2-VASc > $CHADS_2$ in "truly low risk" subjects (Thromb Haemostasis 2012;107:1172)
  - Score 0 = no AC or ASA; Score 1 (2 in women)= no AC vs AC based on clinical judgment, generally lean towards AC initiation; Score ≥2 (≥3 in women) = AC

Yichi Zang

- NOT used to guide decision making for HOCM or mitral stenosis (MS) with moderate severity or greater.

- **HAS-BLED**: risk stratification of bleeding risk w/ oral AC. HTN (SBP>160); abnl renal function (CrCl<50); liver disease (cirrhosis or Bili 2x ULN or AST/ALT/AlkPhos 3x ULN); stroke; bleeding history; labile INR (<60% in Rx range); elderly (>65y); antiplatelet meds (ASA, NSAID); alcohol (>8 drinks/w) or other drug use. Score ≥3 suggests caution and regular follow-up
- SPARCtool can aid in risk/benefit assessment and choice of anticoagulation

Anticoagulation (AHA/ACC/HRS: Circ 2024; 149: e1-e156 ; Stroke 2010;41:2731)

- Consider AF burden when estimating stroke risk (JAMA Card 2018; 601-608). Subclinical AF is also associated w/ increased stroke/systemic embolism (NEJM 2012;366:120). In these pts, AC reduces the risk of ischemic stroke but increases the risk of major bleeding, thus AC decision should be individualized. (Circ 2023; 123:067512)
- **DOACs vs warfarin**: DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) recommended > warfarin in all except w/ mod-severe mitral stenosis, HOCM, or mechanical valve. Warfarin may be > rivaroxaban in rheumatic heart dz (NEJM 2022;387:978-988). DOACs: ↓risk of stroke, mortality, & ICH, ↑risk of GIB (Lancet 2014;383:955), apixaban lowest GIB risk (Annals 2022:175:1515-1524)
- **Dosing**: see *Anticoagulation Agents* for dosing. Dose-reduce apixaban to 2.5mg BID if 2/3: Cr ≥1.5, Wt ≤60kg, age ≥80
- **Renal impairment**: for pts w/ CrCl<15 or on dialysis, can use either warfarin or apixaban
- **Bridging AC**: see *Anticoagulation Management*

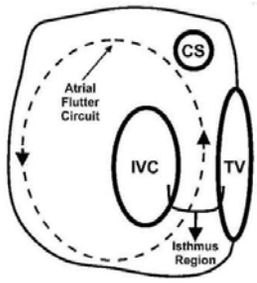
- **Left Atrial Appendage Occlusion (LAAO) -** LAA is the source of at least 90% of thrombi in pts with CVA and AF
- **Watchman device**: in non-valvular AF, device placement → comparable stroke prevention to warfarin with ↓bleeding risk & improved mortality (JACC 2017;70:2964). Consider if contraindication to long-term AC. AC can be discontinued 6w after LAAO, per MGH protocol.
- **Surgical occlusion**: decreases risk of stroke and systemic embolism. Grade 1A recommendation for pts with CHA_2DS_2-VASc ≥2 undergoing cardiac surgery in addition to continued AC (Circ 2024; 149: e1-e156).

Long-Term Rate vs Rhythm Control

- Traditionally, rate control considered noninferior to rhythm control for AF sx, CV mortality, & stroke risk (AFFIRM, RACE, PIAF, STAF, HOT CAFÉ, AF-CHF). Latest guidelines shifted with benefit of early rhythm control and reducing AF burden. (Circ 2024; 149: e1-e156)
- **Rhythm control** (antiarrhythmics and AF ablation) superior to usual care (rate control) for patients with recently diagnosed AF (within 1 year) and concomitant CV conditions in decreasing CV mortality, stroke, and hospitalization for HF or ACS (EAST-AFNET 4)
  - Consider **rhythm control** if persistent AF sx impairing quality of life, age <65, or comorbid HF (esp if systolic dysfxn)
  - Restoration of NSR may lead to increased quality of life & exercise performance (NEJM 2005;352:1861; JACC 2004;43:241)
- **Rate Control**
  - **BB > CCB** in achieving rate control (70% vs 54%), either alone or in combination with digoxin
  - **Digoxin** alone is moderately effective in controlling V-rate at rest (time to onset 3-6 hrs), ineffective w/ high adrenergic tone
    - Long-term digoxin a/w increased mortality in AF patients (JACC 2018;71:1063)
  - **Targets**: lenient rate control (resting HR <110) non-inferior to strict (HR <80) w/ similar outcomes in CV death, stroke, bleeding, arrhythmia, & hospitalization for HF (RACE II). Strict HR (or rhythm) control may be beneficial in younger pts or pts w/ HF
  - Contraindications/Warnings: evidence of pre-excitation on ECG (in these patients, IV procainamide is 1st line), cautious use in high-degree AVB. CCB should not be used in pts with LVEF <40% given negative inotropy
- **Rhythm Control** (Circ 2012;125:381)
  - **Choice of Agents**:
    - No structural heart disease: "pill-in-pocket" (flecainide/propafenone), dofetilide, dronedarone, sotalol, amiodarone
    - Structural heart disease: **CAD**: dofetilide, dronedarone, sotalol, amiodarone; **HF or LVH**: amio, dofetilide
  - **"Pill-in-Pocket"**: for pts with recent pAF and infrequent and well-tolerated episodes, ppx may have risk>benefit. PRN flecainide or propafenone + BB or CCB at sx onset is safe and effective (NEJM 2004;351:2384)
  - **Catheter ablation** (pulmonary vein isolation [PVI]): ↓long-term AF recurrence rate vs AADs in both pAF (MANTRA-PAF, RAAFT-2) & persistent AF (EHJ 2014;35:501). Ablation in pts w/ HF ↓morbidity/mortality (CASTLE-AF). Ablation improves psychological distress. (JAMA 2023; 925-933)
  - **AV nodal ablation with PPM**: indicated when pharmacologic rate/rhythm control not achievable (JACC 2014;64:2246)

ATRIAL FLUTTER (AFL, less prevalent but often coexists with or precedes AF)

- ECG: "sawtooth" P waves (F waves), atrial rate typically 250-300bpm w/ 2:1 conduction (~V-rate 150), though can be variable block, 3:1, or 4:1. 1:1 conduction can briefly precede VT/VF
  - **Type 1 (typical)**: reentrant loop in RA via cavo-tricuspid isthmus
    - Counterclockwise: more common, inverted flutter waves II, III, aVF + upright flutter waves V1
    - Clockwise: less common, upright flutter waves in II, III, aVF + inverted flutter waves in V1
  - **Type 2 (atypical)**: does not meet criteria for Type 1; is often faster and refractory to ablation
- **Anticoagulation**: risk of thromboembolism lower than AF (J Stroke Cerebrovasc 2018;27:839) but anticoagulation management is similar to AF (Chest 2012;141:e531S)
- **Rate control**: similar strategies (BB, CCB) to AF, but more difficult to successfully rate-control vs. AF
- **Rhythm control**: Ablation **> AAD.** Cavo-tricuspid isthmus (CTI) ablation for typical flutter >90% effective at 1y (Circ Arrhythmia EP 2009;2:393). However, prophylactic CTI ablation during PVI for AF pts without documented AFL fails to reduce incidence of AFL or recurrence of AF (Arryth EP Rev 2022; e10).

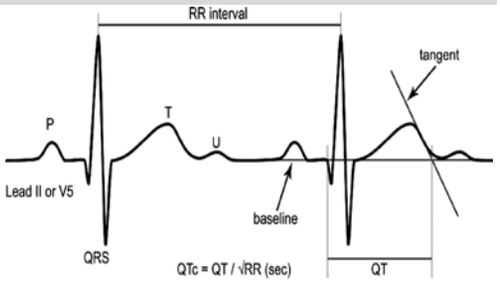


Cardiology

QTc Prolongation

Definition (Circ 2009; 119: e241)

- QT interval correlates with repolarization time of ventricles
- Normal: ≤460ms; Borderline (adult): 460-479ms (female), 450-459ms (male)
- Measure from beginning of QRS to end of T wave in a lead with T wave > 2mm (best in II, V5), define end point using tangent from peak of steepest slope to isoelectric line; can use ECG or caliper function on telemetry
- QTc is QT corrected for HR; linear (i.e., Hodges/Framingham) formulas are recommended by AHA (J Electrocardiology 2004;37:81)
- Can be **calculated using MDCalc** or with formulas below:
  Framingham = QT + 0.154 * (1-RR) | Fridericia = QT/$\sqrt[3]{RR}$ | Hodges = QT + 1.75 * (60/RR-60) | Bazett = QT/$\sqrt{RR}$ | Rautaharju = QT * (120+HR)/180
  - **Framingham and Fridericia provide best rate correction and mortality prediction** (JAHA 2016;5:e003264)



Assessment of QTc with Underlying Wide QRS (Heart Rhythm 2014;11:2273)

- Wide QRS (BBB/V-paced) lengthens QT interval; **calculate using Mayo calculator,** or with rough estimate using QT - (QRS-120)
  - JT prolongation index = JT * (HR + 100)/518 where JT is distance between J point and end of T, with a JTI ≥112 identifying repolarization prolongation in all ventricular conduction defects (J Electrocardiology 1992;25;131)

Congenital Long-QT Syndromes

- Majority of pts are asymptomatic, often discovered on ECG or QTc prolonged more than should be expected by drugs, etc.
- Sx: presyncope/syncope, hemodynamic compromise, sudden cardiac death; triggered by exercise, stress
- Tx: beta blockers, ICD if previous cardiac arrest and expected survival >1y (Circ 2006;114:e385)

Drug-Induced Prolonged QT Interval (Heart 2003;89:1363; NEJM 2004;350:1013)

- Drugs inhibit I_{Kr} causing prolonged ventricular repolarization & exaggerate heterogeneity in repolarization times in different layers of myocardium leading to reentry and tachyarrhythmia

Danger of prolonged QT = increased risk of Torsades de Pointes (TdP), which can degenerate into VF
Longer QT increases risk for "R on T" phenomenon and development of TdP (higher risk if PVCs)

Risk factors for TdP in Hospitalized Pts (Circ 2010;121:1047)	
Demographics	Elderly, female, congenital LQTS, anorexia/starvation, hypothermia
Comorbidities	Renal failure, hepatic dysfunction (or drug-drug interactions impairing liver metabolism), HF, MI, LVH, hypothyroidism
Rhythm-related	**QTc >500ms,** bradycardia (sinus, AV block, ectopy causing pauses), **PVCs**
Electrolytes	**Hypomagnesemia**, hypokalemia, hypocalcemia
Medication-related	QT-prolonging **drugs** (esp. IV infusions, >1 concurrently), diuretic use, beta blocker use

Class of Drug	QT-Prolonging Drugs: [**common**, *high-risk*, (low-risk)] (Br J Clin Pharm 2010;70:16; Circ 2020:142:e214)
Antiarrhythmics	CLASS IA/C: *quinidine*, *disopyramide*, *procainamide*, flecainide, propafenone CLASS III: ***sotalol***, ***dofetilide***, *ibutilide*, *dronedarone*, ***amiodarone*** - oral amiodarone rarely associated w/ TdP due to uniform delay in repolarization across myocardium
Antimicrobials	ANTIBIOTIC: **azithromycin**, erythromycin, clarithromycin, **levofloxacin**, moxifloxacin, (**ciprofloxacin**), (**metronidazole**) ANTIFUNGAL: **fluconazole**, voriconazole, (**ketoconazole**) ANTI-MALERIAL: *quinine*, *quinidine*, chloroquine, (hydroxychloroquine)
Antipsychotics	***haloperidol IV***, *thioridazine*, *chlorpromazine*, *ziprasidone*, **quetiapine**, **risperidone**, **olanzapine**, haloperidol oral, clozapine
Antidepressants	Clomipramine, imipramine, **citalopram, escitalopram, (fluoxetine), (sertraline), (trazodone)**, (mirtazapine)
Anti-emetics	**ondansetron IV>oral**, droperidol, (**metoclopramide**)
Others	***Methadone***, **propofol**, **hydroxyzine**, (**loperamide**), (**albuterol**), (donepezil)

Monitoring for QT/QTc Prolongation

- Check QTc before and 12h after initiation/increased dose of QT-prolonging drug. Continue monitoring if prolongation is seen.
  - Check QTc 2h post loading-dose of sotalol or dofetilide
- Class I indications for QTc monitoring with ECG (Circ 2004;110:2721)
  - Initiation of QT-prolonging medication and dose changes q8-12h
  - Overdose of proarrhythmic drug
  - New bradyarrhythmia
  - Severe hypokalemia or hypomagnesemia

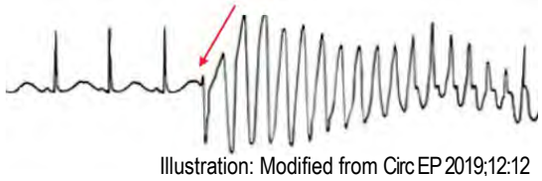


Illustration: Modified from Circ EP 2019;12:12

Management of Acquired Long QT

- **Stop offending drug** if **QTc >500ms** or **increase in QTc of >60ms**
- ECG should be checked for bradyarrhythmias & signs of impending TdP (R on T, above). Stop drugs causing bradycardia.
- Check electrolytes & consider repleting (K >4, Mg >2). Supratherapeutic repletion (K: 4.5-5, Mg: 2-2.5) can be if risk of TdP

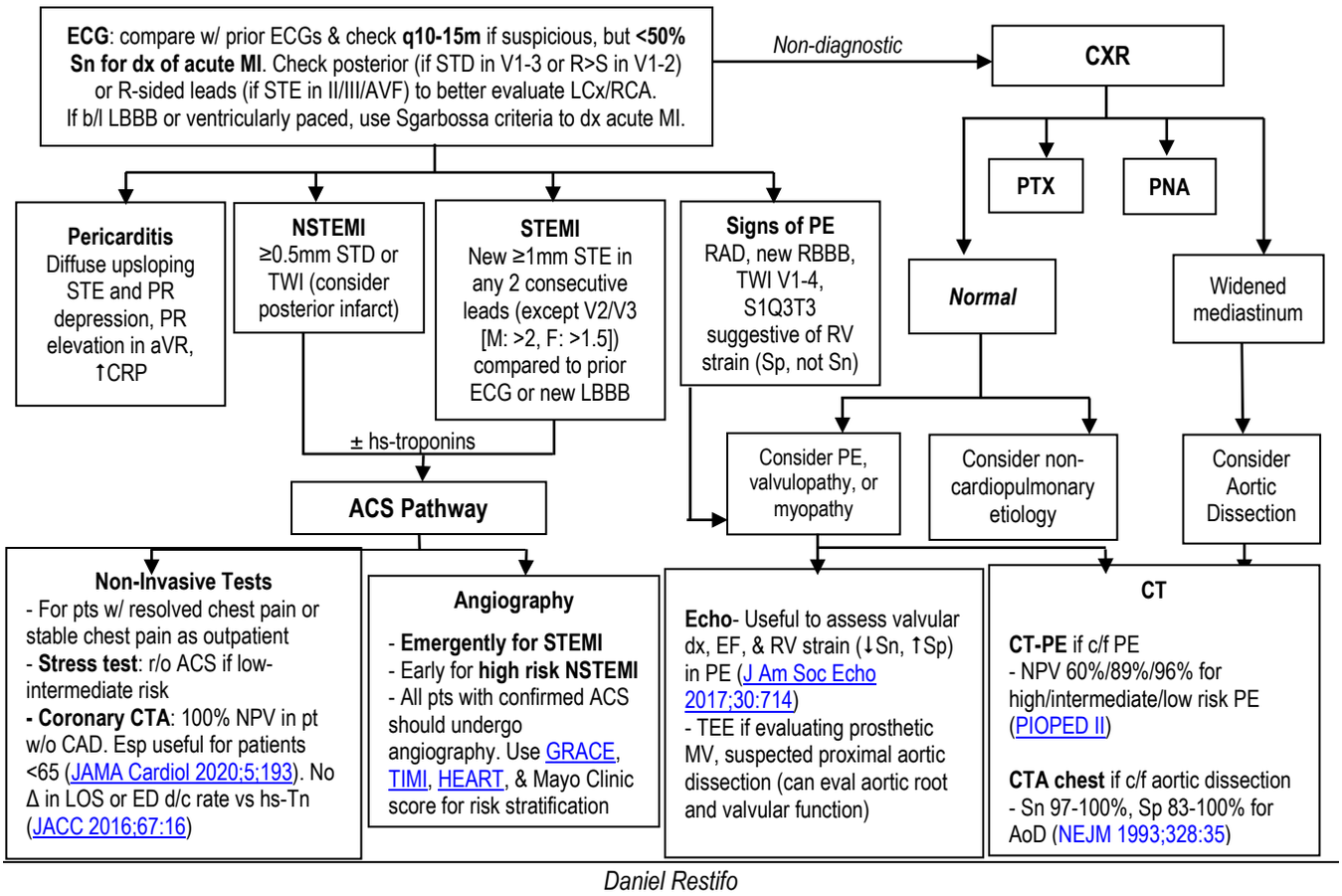
Erika Kaske

Cardiology

Chest Pain

	History	Physical Exam
Stable Angina/ACS (Circulation 2021;22;e368) *Symptoms are no longer described as atypical/typical, instead use cardiac, possible cardiac, or noncardiac (Circulation 2022;80(17))	**Assess:** Characteristics and duration of symptoms, associated symptoms, provoking factors, and CVD risk factors. **Classic angina triad*:** (1) **substernal** chest pain, (2) worse w/ **exertion**, and (3) **relieved by rest or nitrate** *Anginal Equivalents*: Chest pain/ pressure/tightness, discomfort in chest/ shoulders/arms/neck/back/upper abdomen/ jaw, SOB and fatigue **Women**, **elderly** and **pts w/ DM** may have vague sx: palpitations, jaw/neck/back pain, SOB, N/V, abd pain, (pre-) syncope, AMS **Antianginals**: nitrates; avoid if preload sensitive (HoTN, AS, recent PDEi); BB (careful in ADHF, long PR, 2˚/3˚ AV block); CCB if BB intolerant; ranolazine Likelihood Ratios for ACS (JAMA 2015;314:1955) **Low Risk**: Pleuritic (0.3); Syncope (0.5) **Intermediate Risk**: Radiation to left arm, neck, or jaw (1.3-1.5); Diaphoresis (1.4); exertional (1.5); Pressure / typical (1.9); Pattern change / 24h (2.0) **High Risk**: Similar to prior ischemia (2.2); Pain radiating to both arms (2.6); PAD (2.7); Abnormal prior stress test (3.1) N.B.: Significant racial/ethnic disparities exist in dx of ACS.	• Distress, diaphoresis • **New S4**, MR (*ischemia*) • **CHF** (crackles, +S3, ↑JVP, pedal edema) • Carotid, subclavian, & abdominal bruit (indicates vascular disease) • Bilateral femoral and radial pulses (*document pre-cath*) • Frank's sign: bilateral diagonal earlobe crease (slight ↑ in likelihood of CAD in adults <60yrs) • Less likely ACS: **p**leuritic, **p**ositional, re**p**roducible by **p**alpation (LR 0.28)
Acute Aortic Syndromes	**Abrupt onset** of tearing/sharp thoracic or abdominal pain RF: known aneurysm, Marfan syndrome, CTD, HTN, M:F 2:1, 60-80y, cocaine use, high-intensity exertion (weightlifting)	BP variation >20mmHg between arms, pulse deficits, new diastolic murmur, focal neurologic changes
Acute Pericarditis	Pleuritic, sharp, improves upon leaning forward May have URI prodrome; consider bacterial pericarditis if high fevers	Friction rub (*breath hold to distinguish from pleural rub*); tamponade (pulsus >10 mmHg)
PE	Sudden onset, dyspnea/hypoxemia, pleuritic RF: hx of cancer/recent surgery/immobility, hemoptysis, calf/thigh pain/swelling	Tachycardia, tachypnea, hypoxemia, calf/thigh erythema, swelling, tenderness
Pneumothorax	Sudden onset dyspnea; RF: 20-40y (more likely if tall), FH or personal history, smoker, known emphysema, M > F, recent chest procedures/lines	Ipsilateral absence of breath sounds, contralateral deviation of trachea
Pneumonia, Pneumonitis	Sharp, pleuritic CP a/w fever/↑WBC, productive cough, recent radiation, autoimmune (SLE, RA, drug-induced lupus, collagen vascular diseases)	Bronchial breath sounds, crackles, dullness
Other	**Cardiac**: HOCM, AS, vasospasm (Prinzmetal's, drug/toxin), Takotsubo; **MSK**: costochondritis, Zoster; **GI:** GERD, esophageal spasm (may be relieved by TNG), Boerhaave's, PUD, biliary colic, pancreatitis; **Psych**: panic attack	

Basic Chest Pain Algorithm


ECG: compare w/ prior ECGs & check q10-15m if suspicious, but <50% Sn for dx of acute MI. Check posterior (if STD in V1-3 or R>S in V1-2) or R-sided leads (if STE in II/III/AVF) to better evaluate LCx/RCA. If b/l LBBB or ventricularly paced, use Sgarbossa criteria to dx acute MI.
Non-diagnostic
CXR
PTX
PNA
Normal
Widened mediastinum
Pericarditis
Diffuse upsloping STE and PR depression, PR elevation in aVR, ↑CRP
NSTEMI
≥0.5mm STD or TWI (consider posterior infarct)
STEMI
New ≥1mm STE in any 2 consecutive leads (except V2/V3 [M: >2, F: >1.5]) compared to prior ECG or new LBBB
Signs of PE
RAD, new RBBB, TWI V1-4, S1Q3T3 suggestive of RV strain (Sp, not Sn)
± hs-troponins
ACS Pathway
Consider PE, valvulopathy, or myopathy
Consider non-cardiopulmonary etiology
Consider Aortic Dissection
Non-Invasive Tests
- For pts w/ resolved chest pain or stable chest pain as outpatient
- Stress test: r/o ACS if low-intermediate risk
- Coronary CTA: 100% NPV in pt w/o CAD. Esp useful for patients <65 (JAMA Cardiol 2020;5:193). No Δ in LOS or ED d/c rate vs hs-Tn (JACC 2016;67:16)
Angiography
- Emergently for STEMI
- Early for high risk NSTEMI
- All pts with confirmed ACS should undergo angiography. Use GRACE, TIMI, HEART, & Mayo Clinic score for risk stratification
Echo- Useful to assess valvular dx, EF, & RV strain (↓Sn, ↑Sp) in PE (J Am Soc Echo 2017;30:714)
- TEE if evaluating prosthetic MV, suspected proximal aortic dissection (can eval aortic root and valvular function)
CT
CT-PE if c/f PE
- NPV 60%/89%/96% for high/intermediate/low risk PE (PIOPED II)
CTA chest if c/f aortic dissection
- Sn 97-100%, Sp 83-100% for AoD (NEJM 1993;328:35)

Daniel Restifo

Cardiology — Acute Coronary Syndrome

Definitions and Evaluation

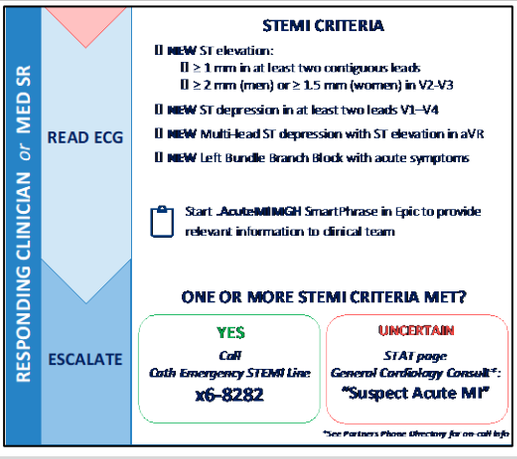
Myocardial injury: defined as any patient with troponin >99th percentile without evidence of myocardial ischemia (sx of ischemia, new ischemic ECG changes, new wall-motion abnormalities, and/or acute coronary thrombus on angio). May be acute or chronic.

Myocardial infarction: myocardial necrosis (trop >99th percentile + Δ) w/ ischemia (4th universal def. of MI, types 1-5: JACC 2018;72:2231)

- Type 1 MI: spontaneous plaque rupture, erosion,→intraluminal thrombus
- Type 2 MI: supply-demand mismatch that is not atherothrombosis – most commonly due to sepsis/infection, arrhythmias, severe anemia, renal failure, surgery, hypertension, and heart failure; other causes include vasospasm, microvascular ischemia (e.g. Takotsubo), thromboembolism (Circulation 2019;140:1661).
  - Must have a ***clear*** precipitating factor. If not, treat as a type 1 MI until further evaluation
  - 50-70% have obstructive CAD – reasonable to initiate ASA, BB, and high-intensity statin

Evaluation of CP with hsTnT	
Emergency Department – CP onset ≥3h PTA	**Inpatient or Emergency – CP onset < 3h**
Check hsTnT **immediately** and at **1h**	Check hsTnT **immediately** and at **3h**
Rule in: hsTnT ≥52 OR Δ ≥5 from baseline → **consider ACS**	Rule in: hsTnT ≥10 (F) or ≥15 (M) AND 3h ΔTn ≥7 from baseline AND sx or ECG changes or concerning imaging (CCTA, cath) → **consider ACS**
Rule out: hsTnT <10(F) or <12(M) AND Δ <3 from baseline → **unlikely ACS**	Rule out: no significant Δ in 3h → **unlikely ACS**
Intermediate: calculate HEART score, repeat hsTnT in 3h and apply inpatient criteria	

STEMI	NSTEMI	Unstable Angina
• 1mm STE in two contiguous leads (if V2-V3: >2.5mm in M<40, 2mm in M>40, 1.5mm in F) OR new LBBB AND ⊕ biomarkers • If baseline LBBB, use Sgarbossa's criteria: ≥1 mm concordant STE, 1 mm STD V1-V3, ≥ 5 mm discordant STE • Electrically Silent: LCx or RCA lesions. Consider posterior V7-V9 leads, in which STE>0.5mm is diagnostic. Other changes: large R in V2-V3, STdep in anterior leads (mirror image effect)	⊕ ECG or hx, ⊕ biomarkers	⊕ ECG or hx, ⊖ biomarkers


RESPONDING CLINICIAN or MED SR
READ ECG
ESCALATE
STEMI CRITERIA
NEW ST elevation:
≥ 1 mm in at least two contiguous leads
≥ 2 mm (men) or ≥ 1.5 mm (women) in V2-V3
NEW ST depression in at least two leads V1–V4
NEW Multi-lead ST depression with ST elevation in aVR
NEW Left Bundle Branch Block with acute symptoms
Start .AcuteMIMGH SmartPhrase in Epic to provide relevant information to clinical team
ONE OR MORE STEMI CRITERIA MET?
YES
Call
Cath Emergency STEMI Line
x6-8282
UNCERTAIN
STAT page
General Cardiology Consult*:
"Suspect Acute MI"
*See Partners Phone Directory for on-call info

Clinical Evaluation & Risk Stratification:

- Consider pt's baseline CAD risk. Review prior stress test and cath data. ↑risk of MI w/ resp infxn (esp flu) (NEJM 2018;378:345)
- Treat secondary causes of myocardial demand

ECG: (NEJM 2003;348:993)

- Obtain serial tracings (q15-30min) if initial ECG non-diagnostic in pts with compelling hx & sx
- Non-STE ischemic EKG changes: ≥0.5mm STD (horizontal, downsloping), new TWI ≥1mm or normalization ("pseudonormalization") of prior TWI in s/o sx

Cardiac Biomarkers:

- hsTnT 99th %ile among normal subjects: M 15ng/L, F 10ng/L
- 75% of healthy individuals will have measurable hsTnT
- hsTnt peaks within 12-48 hrs, normalizes in 5-14 days

Revascularization

STEMI

- Primary PCI (PPCI) recommended revasc strategy for pts w/STEMI <48h symptom onset
- PCI center: aim<60 min to wire crossing; non-PCI center: aim<90 min to wire crossing
- PPCI regardless of symptom onset if cardiogenic shock, malignant arrhythmia (recurrent sustained VT/VF), persistent STE and/or CP.
- PPCI>48h symptom onset not indicated in stable pts (NEJM 2006;355:2395)
- If PPCI not possible within 120 min FMC (and <24h symptom onset), fibrinolysis: Aim<10 min to lytic bolus (Tenecteplase preferred) w/ immediate transfer to PCI center. Discuss antithrombotic therapy w/cardiology. Contraindicated in ↑bleeding risk (esp ICH), suspected dissection, ischemic stroke <3 months prior, severe HTN

NSTE-ACS (NSTEMI/UA)

- Multiple risk models incl GRACE, TIMI, PURSUIT. GRACE score is based on predictors of 6mo mortality (age, HR, SBP, Cr, cardiac arrest at admission, ST deviation, elevated trop) (BMJ 2006;333:1091)
- Four subgroups for urgency to revascularization (JACC 2014;64:e139)
  1. **Very high risk** ("immediate invasive," within 2h): **refractory/recurrent angina, hemodynamic or electrical instability, mechanical complications, recurrent dynamic ECG changes suggestive of ischemia**
  2. **High risk** ("early invasive," within 24h): temporal change in troponin, ECG changes (transient STE, STD, TWI), high risk pt (GRACE>140)
     a. Conflicting results between TIMAC (NEJM 2009;360:2165) and VERDICT (Circ 2018;138:2741) trials about outcome benefit of early cath. However, both show improved outcomes with early cath in patients with GRACE >140
  3. **Intermediate risk** ("delayed invasive," within 72h): none of above but risk factors at baseline (e.g. EF <40%, GFR <60)

4. **Low risk** ("ischemia guided," no cath): no risk factors, GRACE <109, TIMI 0-1 OR not good candidate for angiography

PCI vs CABG: Selection of revascularization strategy should be based on the acuity of the patient's condition, the angiographic characteristics of the culprit lesion, and the complexity of the patient's anatomy and, when appropriate, should include a Heart Team discussion (Guideline: Circulation 2022;145:4). CABG often preferred for 3VD (NEJM 2009;360:961), L main disease (Lancet 2016;388:2743; NEJM 2016;375:2223), 2VD with prox LAD stenosis or EF <50%, DM + 2VD w/ involvement of LAD (NEJM 2012;367:2375).

Multivessel Disease PCI Strategies

- STEMI w/o cardiogenic shock: complete revascularization strategy (culprit + non-culprit) has ↓risk of CV death and MI at 3y (COMPLETE, NEJM 2019;381:1411)
- STEMI OR NSTE-ACS + cardiogenic shock: culprit-lesion only PCI has a ↓risk of death/RRT (CULPRIT-SHOCK, NEJM 2018;379:1699). Consider staged complete revascularization
- NSTE-ACS w/o cardiogenic shock: complete revascularization strategy (BIOVASC, Lancet 2023;401:1172)

Adjuncts to Revascularization

Adjuncts at Presentation:

1. **ASA**: established mortality benefit, give to all pts in an immediate load/maintenance strategy (325mg/81mg) (Lancet 1988;2:8607)
2. **Peri-Intervention Anticoagulation**: start on Dx of ACS. Usually stopped after PCI if no additional indication for AC (eg Afib, PE). If no PCI and medically managed, usually d/c at 48h if ECG changes improving and c/f ongoing ischemia resolved (BMJ 1996;313:652). If chronically on warfarin/DOAC, discuss transition to short acting AC with pharmacy pre-cath.
   - **UFH**: Standard. Start gtt w/ bolus and use **low intensity PTT goal** (63-83). No bolus if giving lytics or if on warfarin and INR<2
   - **LMWH**: possible reduction in death w/ minimal evidence for ↑major bleeding, trials vs UFH largely null (BMJ 2012;344:e553)
   - **Fondaparinux**: preferred to UFH/LMWH if medically managed. Contraindicated in PCI ↑catheter thrombosis/complications (JAMA 2006;295:1519)
   - **GPIIb/IIa Inhibitors**: eptifibatide (Integrilin) used at MGH. Initiated in cath lab if PCI high-risk (extensive thrombus)
   - **Bivalirudin/Argatroban**: direct thrombin inhibitor, preferred for patients w/ HIT. Emerging evidence suggests benefit over UFH in STEMI (BRIGHT-4 Lancet 2022;400:1847)
3. **Statin**: atorvastatin 80mg daily regardless of baseline LDL (NEJM 2004;350:1495)
   - Early high-dose statin within 24-96h may reduce death/adverse cardiac events if given pre-PCI (JACC 2009;54:2157; JAMA 2018;319:1331). Early anti-inflammatory effect may stabilize plaque (JAMA 2001;285:1711; JAMA 2004;291:1071)
   - If very high risk clinical ASCVD w/ LDL-c>70 mg/dL, add **ezetimibe** and consider PCSK9i (JACC 2019;73:3168)
4. **Nitrates**: TNG SL (0.3-0.6mg) x3, if refractory → gtt (start 5-10mcg/min titrate to chest pain free). Nitropaste and gtt have shorter half-life than SL if c/f HoTN. No mortality benefit. Caution in inferior MI/RVMI, SBP<100, or PDEi use in last 48h. If refractory CP indication for earlier cath.
5. **Morphine**: not recommended. Consider only if unacceptable level of pain refractory to TNG, careful if suspicious for inferior MI/RVMI
6. Discontinue NSAIDs: ↑risk of mortality, re-infarction, HF, and myocardial rupture after ACS

Adjuncts to start within 24h or Post-Revasc

7. **P2Y12 Inhibitors*: Pre-cath load not done at MGH. Do not start w/o cards***. Controversial benefit & may delay CABG by 5-7d (Circulation 2022;145:4).
   - Ticagrelor: ↓mortality compared to clopidogrel w/o increasing major bleeding. Reversible with platelet transfusion. Side effect: **dyspnea** (14-21%, often mild & transient, but can be severe enough to warrant discontinuation), risk of pneumonitis w/ alveolar hemorrhage. Avoid in liver disease, prior CVA, oral AC (PLATO, NEJM 2009;361:1045).
   - Prasugrel: ↓death, MI, CVA compared to ticag (NEJM 2019;381:1524). Contraindicated if prior TIA/CVA, wt <60kg, or >75y
   - Clopidogrel: ↓death, repeat MI when load/maintenance with PCI (Lancet 2001;358:527I). Prodrug, metabolized by CYP219, less effective in those with LOF allele (NEJM 2009;360:354). May benefit from PPI ppx for ↓UGIB (NEJM 2010;363:1909). ↓Bleeding compared to ticagrelor and prasugrel but ↑ischemic events (Circulation 2020;142:150).
   - Cangrelor: IV reversible inhibitor with immediate onset and return of platelet function in 1h. Used in pts with recent PCI who are unable to take PO or are periprocedure, needs pharmacy approval

   DAPT duration: Default 12 months after ACS. Use DAPT score to help risk stratify. Evolving movement to shorten DAPT duration (TWILIGHT NEJM 2019;381:2032; TICO JAMA 2020:323:2407; STOPDAPT-2 JAMA 2019;321:2414; SMART CHOICE JAMA 2019;321:2428; GLOBAL LEADERS Lancet 2018;392:940-949; MASTER DAPT NEJM 2021;385:1643-1655 HOST-EXAM Lancet 2021;397:2487).
   Bottom line: In select patients, single agent P2Y12 inhibitor after 1-3 months (vs. longer duration DAPT) is non-inferior in reduction of cardiovascular events, with reduced bleeding risk.
   - **If on longterm AC (eg AFib, PE)**: P2Y12 inhibitor + DOAC > triple therapy. ↓bleeding and non-inferior for ischemic events (AUGUSTUS NEJM 2019;380;1509; RE-DUAL PCI NEJM 2017;377:1513; NEJM 2016; 375:2423). (Guideline JACC 2021;77:629).
     - Common example: initiate triple therapy (ASA/clopidogrel/AC) for 1-4wks and then d/c ASA → AC + clopidogrel
8. **Beta Blockers**: start within 24h (1B for STEMI, 1A for NSTE-ACS), mortality benefit. Consider early initiation if ischemic arrhythmias present. Not indicated for stable ischemic heart disease s/p cath, but rec'd after CABG (Circulation 2022;145:4)
   - Caution in decompensated HF, ↑risk for cardiogenic shock (>70y, SBP <120, HR >110 or <60)
   - Contraindications: shock, cocaine-induced MI, PR>240ms, 2nd or 3rd degree AVB, severe bronchospasm (Lancet 2005;366:1622)
9. **ACEi or ARB**: start ACE within 24h in all patients if BP/renal function normal (2a;LOE:A for STEMI) but mortality benefit (1; LOE:A) in anterior STEMI; use ARB if intolerant of ACE. ARB > ACE in patients with HF or LVEF <40% (Circulation 2008; 117:269).
10. **Aldosterone antagonist:** s/p MI on ACE and BB, and have LVEF<=40 + DM or sx of HF (1;LOE:B) (Circulation 2008; 117:269)
11. **Lifestyle**: smoking cessation, BP <140/90 (if DM or CKD, <130/80), cardiac rehab (1; LOE:B), depression screening; Flu vaccination

MGH P2Y12 Switching Guidelines (Ellucid policy, does not apply to patients on triple therapy)

Cardiology

MI Complications

MECHANICAL COMPLICATIONS (JACC 2013;61:e78; JACC Cardiovasc Interv 2019;12:1825)

	Complication	Prevalence / Risk Factors	Timing / Clinical Signs	Evaluation	Treatment
EARLY COMPLICATIONS (Hours – Days)	**Cardiogenic Shock** (see *Inpatient HF*)	▪ STEMI~6%, NSTEMI~3% ▪ Anterior MI, LBBB, prior MI, 3VD, age, HTN, DM, mechanical complications ▪ 50% of post-MI death	▪ STEMI: 50% develop shock w/in 6h of MI, 75% w/in 24h ▪ NSTEMI: 72-96h after MI ▪ New CP, cold/wet physiology, HoTN, tachycardia, dyspnea, JVD, rales, new murmur	▪ **TTE** ▪ PAC (CI<2.2, PCWP>18) ▪ End organ hypo-perfusion (lactic acidosis, AKI)	▪ Inotropes/pressors ▪ Emergent PCI/CABG (<75y + STEMI + shock w/in 36h of MI). SHOCK trial (NEJM 1999;341:625) ▪ IABP and other MCS
	Myocardial Free Wall Rupture (Pseudoaneurysm: LV defect contained by only pericardium, scar, more prone to rupture than true aneurysm)	▪ 0.01% STEMIs & NSTEMIs ▪ Transmural MI, 1-vessel MI, 1st MI (poor collaterals), anterior & lateral MI, HTN, late thrombolysis (>14h), fibrinolysis>>PCI, NSAIDs, female, age >70 ▪ 10% post-MI death	▪ 40% w/in 24h, 90% w/in 2w ▪ Tamponade in 85% ▪ Electromechanical dissociation, aberrant T wave evolution, abrupt episodes of ↓HR/BP	▪ **TTE** (pericardial effusion w/ high acoustic echoes indicating clot) ▪ STAT cardiac surgery consult	▪ Emergent surgery for resection of ruptured myocardium w/ primary reconstruction ▪ Fluids, inotropes and pressors (for cardiogenic shock)
	Interventricular Septal Rupture (VSD)	▪ 0.21% STEMIs, 0.04% NSTEMIs ▪ 1st MI, 1-vessel MI (esp. LAD), CKD, anterior infarct w/ inferior STE due to wrap-around LAD, older age, female ▪ 5% of post-MI death	▪ Bimodal: 24h & 3-5d to up to 2w from event ▪ New, harsh holosystolic murmur (50% w/ thrill), S3, loud P2, hypotension, BiV failure (R>L)	▪ **TTE** w/ doppler (L to R shunt, RV overload) ▪ RHC: increase in O2 sat from RA to PA >5, large V waves	Emergency surgery or transcatheter closure device if unstable, mortality ~50%. Closure often delayed if stable. ▪ Vasodilators (use cautiously) to decrease L to R shunt (nitroprusside or nitroglycerin) ▪ IABP/MCS
	Papillary Muscle Rupture (leading to acute MR)	▪ 0.05% STEMIs, 0.01% NSTEMIs ▪ Posteromedial (supplied by PDA, with inf. or post. MI) >> anterolateral (dual blood supply by LAD and LCx) ▪ Poor collaterals, 1st MI, single vessel disease ▪ 5% of post-MI death	▪ No reperfusion: 2-7d ▪ With reperfusion: median 13h ▪ Abrupt dyspnea, pulmonary edema, hypotension ▪ Hyperdynamic LV, holosystolic murmur at apex (radiates to LSB w/ posterior pap muscle rupture), murmur may be absent in torrential MR or severe HF	▪ **TTE** (MR) ▪ CXR: edema (can be asymmetric to RUL if MR jet directed at right pulmonary veins) ▪ Tall *c-v* wave in PCWP tracing	▪ Aggressive afterload reduction (nitroprusside or nitroglycerin) ▪ IABP ▪ Emergent surgery
LATE COMPLICATIONS (Weeks – Months)	**LV Aneurysm** (discrete, dyskinetic area of LV with broad neck, rarely ruptures)	▪ No reperfusion: 10-30% ▪ Apical-anterior wall >> inferior posterior ▪ Total occlusion of LAD ▪ Steroids, NSAIDs	▪ Days to weeks ▪ Acute: diffuse, displaced PMI, S3 and/or S4, MR murmur, CHF ▪ Chronic: HF, VT/VF, systemic embolization, may be asymptomatic	▪ **ECG** w/ persistent STE ▪ **TTE**, other imaging (CMR, CT, ventriculography)	▪ Acute: management of CHF, ACEi, avoid NSAIDs/steroids, start heparin (if EF<35%) ▪ Chronic: ACEi, digoxin, diuretics, AC (if EF<35%) ▪ Surgical repair
	LV Thrombus	▪ 5% of AMI patients post-PCI ▪ Usually in LV apex ▪ Large infarct size, severe apical akinesis or dyskinesis, LV aneurysm, anterior MI	▪ Can form 24-72h post MI ▪ 90% of thrombi are formed by 2w ▪ Embolization risk persists for 6mo but most by 3-4mo; risk 10% if not on AC	▪ **TTE** w contrast ▪ CMR or CT	▪ Warfarin (INR 2-3); DOAC may be a reasonable alternative (Circ. 2022;146:e205–e223) ▪ When to stop AC unclear, check for resolution of thrombus on TTE at 3-6mo
	Pericarditis	▪ Peri-MI pericarditis has decreased with use of reperfusion therapy ▪ Friction rub within 2-3 days post MI. Often large infarct	▪ 10% at 2-4d post-transmural MI ▪ May be focal or diffuseDressler's syndrome (1-6wks): malaise, fever, leukocytosis, late autoimmune carditis, rare	▪ **ECG** (diffuse STE, PR depressions) ▪ **TTE** (effusion) ▪ CMR and/or cardiac CT	▪ ASA + colchicine ▪ Avoid NSAIDs and steroids post MI as can impair infarct healing
	Coronary Artery In-Stent Thrombosis	▪ Highest risk is absence of P2Y12 inhibitor ▪ 1% at 1 year, then ~0.2% per year thereafter	▪ Most cases occur within 30d of PCI irrespective of stent type ▪ ACS symptomatology	▪ **ECG** ▪ Biomarkers (troponin/CKMB)	▪ PCI ▪ Long term anti-platelet therapy (prasugrel or ticagrelor given higher potency) with monitoring of adherence to therapy ▪ DAPT minimum one year

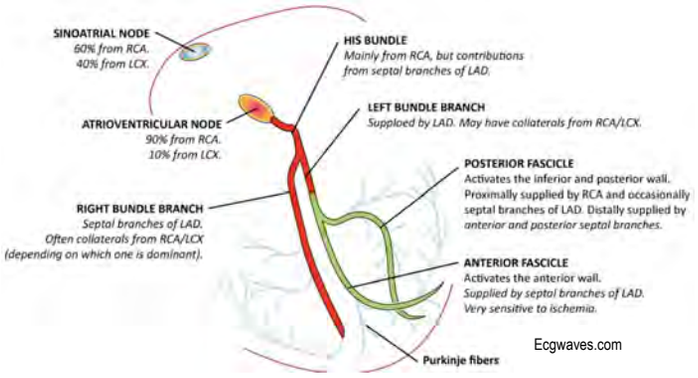
Cardiology

MI Complications

URGENT ASSESSMENT OF POST-MI COMPLICATION (page Cardiology)

- Assess VS for hemodynamic instability, focused physical exam (new murmur, pericardial friction rub, elevated JVP, crackles, access site/s)
- Stat labs (troponin, PT/INR, PTT, T&S, BMP, lactate), ensure adequate vascular access (≥2 PIVs)
- Run telemetry, repeat **ECG**, **STAT TTE**, consider STAT CTA if concern for RP bleed/aortic dissection, notify interventionalist

Circuit	Coronary Vessel Supply
SA Node	60% from RCA, 40% from LCx
AV Node	90% from distal RCA, 10% from distal LCx
Bundle of His	AV nodal artery (RCA), LAD septal perforators
RBB	LAD septal perforators, collaterals from RCA/LCx
LBB	LAD, collaterals from RCA/LCx
LAF	LAD septal perforators (single supply, sensitive to ischemia)
LPF	AV nodal arteries proximally, distally dual supply from LAD/PDA septal perforators

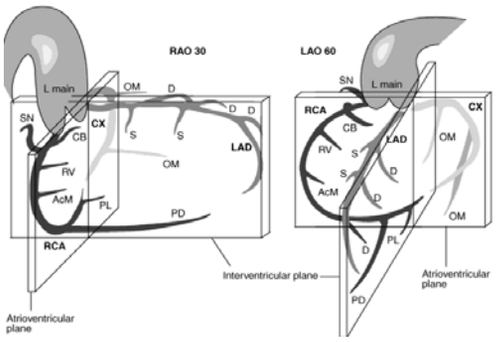

SINOATRIAL NODE
60% from RCA.
40% from LCX.
HIS BUNDLE
Mainly from RCA, but contributions from septal branches of LAD.
ATRIOVENTRICULAR NODE
90% from RCA.
10% from LCX.
LEFT BUNDLE BRANCH
Supplied by LAD. May have collaterals from RCA/LCX.
POSTERIOR FASCICLE
Activates the inferior and posterior wall. Proximally supplied by RCA and occasionally septal branches of LAD. Distally supplied by anterior and posterior septal branches.
RIGHT BUNDLE BRANCH
Septal branches of LAD.
Often collaterals from RCA/LCX (depending on which one is dominant).
ANTERIOR FASCICLE
Activates the anterior wall.
Supplied by septal branches of LAD.
Very sensitive to ischemia.
Ecgwaves.com
Purkinje fibers

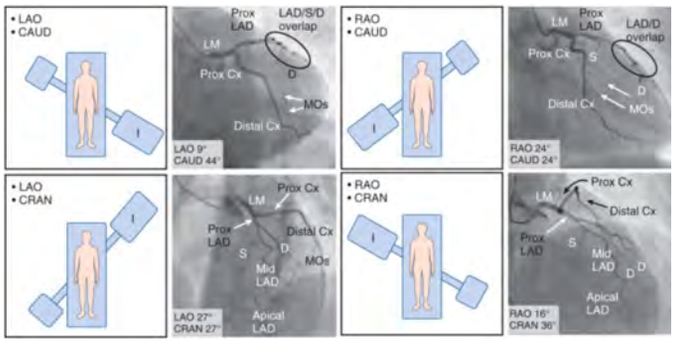
ELECTRICAL COMPLICATIONS

Overview

- Bradyarrhythmia/conduction block: may be due to coronary artery occlusion (see below) or baroreceptor reflexes (Anes 2003;98:1250)
- Tachyarrhythmia: related to creation of re-entrant circuit from scar formation and/or ↑automaticity from adrenergic surge

	Arrhythmia	Location/Mechanism	Incidence/Timing	Treatment/Outcome
Bradyarrhythmia	Sinus bradycardia	▪ Inferior and posterior MI ▪ Beneficial: ↓myocardial O2 demand	▪ Up to 40% of acute MI ▪ Occurs early in STEMI	▪ Atropine, pacing if unstable, dopa/epi if HoTN
	First degree AV block	▪ Inferior: ↑vagal tone *or* AV node ischemia (RCA), narrow QRS ▪ Anterior: septal necrosis below AV node, RBBB, wide QRS	▪ More common in inferior MI	▪ If due to inferior MI, transient (vagal) ▪ Continue CCB or BB unless PR interval >240ms
	Second degree AV block: Mobitz Type I	▪ Usually inferoposterior MI (↑vagal tone, narrow QRS) or AV node ischemia	▪ Usually within first 24h of MI	▪ Usually transient; observe ▪ Atropine if symptoms or HR <45
	Second degree AV block: Mobitz Type II	▪ Usually anterior MI with infranodal conduction injury, wide QRS, HR often <30, 33% progress to CHB	▪ Usually within first 24h of MI	▪ Consider temporary pacing ▪ In infranodal block, *atropine may paradoxically worsen AV block*
	Third degree AV block	▪ If inferior MI: intra-nodal lesion; narrower QRS escape ▪ If anterior MI: infra-nodal lesion; wide, unstable escape rhythm	▪ 3-7% acute MI ▪ Inferior: gradual, stable ▪ Anterior: sudden, 12-24h after MI	▪ Recovery 5-7d; temp pacing required ▪ Inferior: transient, resolves on own ▪ Anterior: carries high mortality rate (80%) and indicates extensive necrosis
Intraventricular Conduction Blocks		▪ 50% already present on first ECG, may represent antecedent disease of conduction syndrome ▪ Suggests more extensive infarct	▪ 2-5% of MI	▪ Patients w/ BBB are more likely to have comorbid conditions, less likely to have received therapies, have larger area infarcts, and have high mortality
Supraventricular Arrhythmias	Sinus tachycardia	▪ May be compensatory for LV dysfunction, common in anterior MI ▪ Pain, anxiety, pericarditis, fever	▪ 25% of acute MI	▪ Undesirable as ↑myocardial oxygen demand, ↓diastole time causes ↓coronary perfusion time ▪ Treat underlying cause
	Atrial fibrillation, Atrial flutter	▪ Early: may be transient due to ↑sympathetic; atrial ischemia ▪ Late: due to atrial stretch/HF	▪ 6-8%, may be >30% of acute MI	▪ A/w mortality, particularly if late (>30d) AF (Circ 2011;123:2094) ▪ If unstable, cardioversion; consider BB, amiodarone, digoxin, anticoagulation
Ventricular Tachyarrhythmias	Premature Ventricular Contraction	▪ Due to electrical instability and increased sympathetic tone	▪ Variable	▪ Correct electrolyte deficits, BB. Do NOT treat with anti-arrhythmics as can ↑mortality (NEJM 1991;324:781)
	Accelerated Idioventricular Rhythm (AIVR)	▪ 50-110bpm, higher V- vs A-rate; in 40%, considered a reperfusion rhythm	▪ Up to 20% of STEMI ▪ Usually within 12-48h, can occur after reperfusion	▪ Do not treat unless symptomatic or hemodynamically unstable, usually short duration & does not affect prognosis
	Ventricular Tachycardia	▪ Monomorphic VT <170bpm is unusual early after STEMI, suggests pre-existing arrhythmogenic scar; recurrent ischemia usually polymorphic VT	▪ NSVT 1-7%, sustained VT (2-3% of STEMI, <1% NSTEMI) ▪ Usually 48h post STEMI, late VT (>48h) has very poor prognosis	▪ Antiarrhythmic agents (amio, lidocaine) ▪ Urgent revasc if due to ischemia ▪ Cardioversion/defibrillation to prevent VF and restore hemodynamic stability ▪ Correct underlying abnormalities (pH, K, Mg, hypoxemia)
	Ventricular Fibrillation	▪ Risk factors: ↑age, prior MI (scar), anterior MI, cardiogenic shock, ↓LVEF, CKD ▪ VF >48h post-MI may indicate LV dysfunction	▪ 5% of STEMI ▪ 1% of NSTEMI	▪ ACLS/defibrillation ▪ Anti-arrhythmic infusion (24-48h amiodarone post-defibrillation) ▪ Maintain K>4, Mg>2.2





- Note: RAO caudal: best overall view & best for LCx; LAO caudal: LM, prox LAD, prox LCx; LAO + RAO cran: mid+distal LAD

Left vs Right Heart Catheterization

- LHC (often used to describe Cor Angio): Arterial access (radial, fem). Assess coronary anatomy/lesions, LV & Ao pressures. PCI.
- RHC: Venous access (IJ, fem). Assess hemodynamics (see *Pulmonary Artery Catherization*); cardiac biopsies (usually RV)

Coronary Anatomy

- LCA and RCA & their branches create two rings around the heart: RCA + LCX in AV groove; LAD + PDA in IV groove
- 80% of PDA arises from RCA (right dominant), thus inferior MI more likely due to RCA lesion; 10% from LCx; 10% co-dominant

Preparation for Catheterization

- NPO MN; INR<2 for radial, <1.8 for fem/IJ; monitor Cr, no ppx abx. Continue ASA (for planned PCIs, loading of 324 mg chewed ASA should be given if pt not on daily ASA), statin, BB. Hold AC (ellucid guidelines): UFH gtt (hold when on call), LMWH (hold tx dose 24h prior. DVT ppx 12h prior), DOACs >48hr or >72hr if CrCl<30. Hold metformin (1d pre-, 2d post-proc), may hold/delay starting ACEi
- Document b/l radial, femoral, popliteal, DP pulses, & Allen's test. Check for bruits. Note history of HIT, PVD, Ao aneurysm/dissection
- **Contrast allergy**: pre-tx w/ steroids & benadryl if patient has documented allergy. See *Contrast Allergy* for MGH protocols.
- Respiratory distress: patient will need to lie flat; consider intubation if prohibitive hypoxemia/pulmonary edema
- Pre-hydration w/ crystalloids and NAC/bicarb have *not* been shown to prevent CIN in most patients with moderate CKD (Lancet 2017;389:1312; NEJM 2018;378:603); CIN risk calculator; See *Contrast*

Percutaneous Coronary Intervention Considerations

- Access: fewer bleeding/vascular complications if **radial** (vs femoral) esp for PCI iso ACS, possible ↓death in ACS (JACC 2018;71:1167); due to radial vasospasm, CCB and/or nitrogylcerin is administered along with UFH to prevent arterial occlusion
- BMS vs DES: **↓in-stent thrombosis with DES** with subsequent ↓MI/revascularization and↓CV death; however, **↑risk of late stent restenosis so requires longer duration of DAPT** (JAHA 2021;10:e018828; Lancet 2019; 393; 2503)
- Can identify HD significant lesions via: fractional flow reserve (FFR), Instant Wave Free Ratio (iFR), intravascular ultrasound (IVUS)
- Contraindications to stents: predicted DAPT non-adherence, anticipated major surgery within treatment time, elevated bleeding risk
- Antiplatelet: 81mg ASA indefinitely (Circ 2016;134:e123). P2Y12 inhibitor added after cath (prasugrel, ticagrelor or clopidogrel)
  - Not high bleeding risk: ACS, 12mo DAPT (DES/BMS); stable IHD, ≥6mo DAPT if DES or ≥1mo if BMS
  - High bleeding risk: ACS, 6mo DAPT (DES/BMS). In select patients, DAPT 1-3 months followed by P2Y12 monotherapy (NEJM 2019; 381:2032); stable IHD, ≥3mo DAPT if DES or ≥1mo if BMS (also consider 1-3mo DAPT followed by P2Y12 monotherapy)
  - Triple therapy: see *ACS*. Usually, 1 wk triple therapy and transition to P2Y12 inhibitor + DOAC.

Post-Procedure Care

- Femoral access: 4-6h bedrest after procedure. Closure devices decrease time needed for bedrest
  - Groin checks immediately, 6h, 8h post-procedure: **check b/l pulses, palpate for pulsatile masses, auscultate for bruits**
  - Sheaths: usually removed when PTT<60, confirm with interventional fellow; **only fellows remove**
- Radial access: TR band for 4-6h. Driven by RN protocol; if paresthesias/numbness, examine, check finger sat probe for perfusion. Can remove several mLs of air from band if necessary and if no complications. NOTE: if hematoma do not remove until fellow assesses.

Post-Catherization Complications

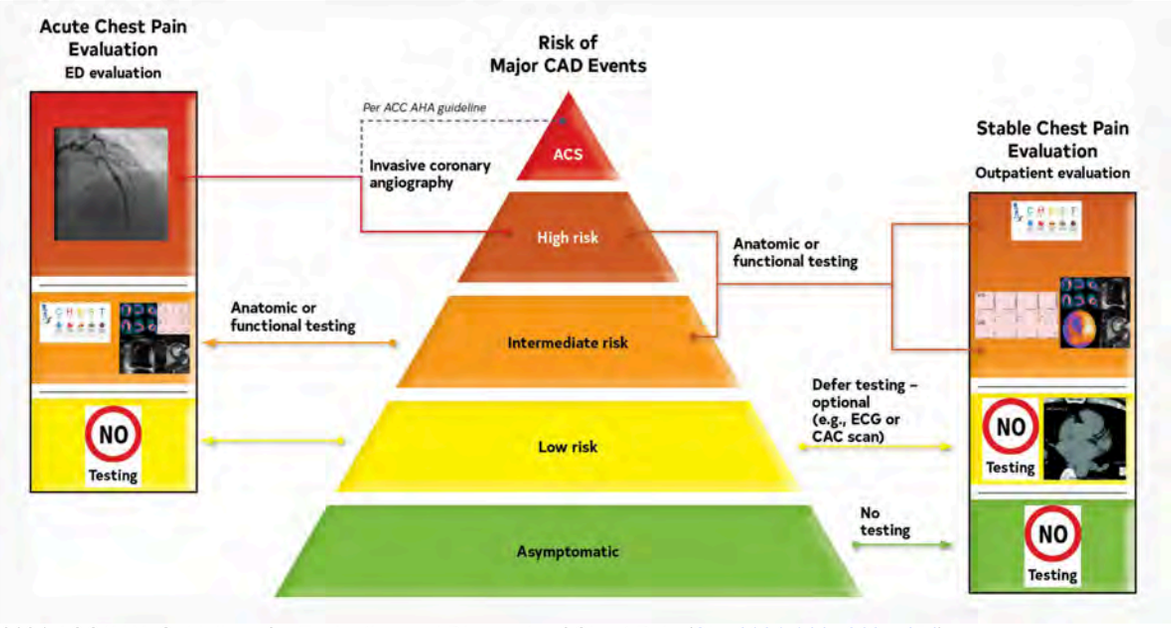
- Access site complications: always inform the interventional fellow who performed the procedure, **diagnose by exam and US**
  - **Hematoma**: mass w/o bruit. Apply **compression**. If unable to control, may require Fem-Stop device to apply external pressure
  - **Pseudoaneurysm**: pulsatile mass with bruit at access site. Tx w/ **compression**; if <2cm, may require thrombin injection or surgery if >2 cm. Urgent US & Vascular Surgery consult
  - **AV fistula**: continuous bruit with no mass. Evaluate w/ US. **Surgical repair** usually necessary
  - **Limb ischemia**: from thrombus, dissection, or malpositioned closure device. Evaluate pulses, limb warmth, & PVR
  - **Retroperitoneal bleed**: presents within **hours** post-cath, often with hemodynamic instability ± flank pain ± ecchymoses. STAT CT A/P if stable. Transfuse, IV fluids, discuss with attending about stopping/reversing anticoagulation
- Other complications:
  - **Infection:** more common in setting of vascular closure devices
  - **Atheroembolism**: eosinophilia; livedo reticularis; blue toes; mesenteric ischemia; acute, subacute, or chronic renal dysfunction
  - **CIN**: occurs within 24-72h with peak Cr 1-5d post contrast load, risk correlated with contrast load and initial GFR
  - **Tamponade**: narrow PP, **hypotension** 2/2 coronary/cardiac perf. Check pulsus (>10 mmHg), STAT echo, page cath fellow.
  - **MI/CVA**: due to in-stent thrombosis (MI) or distal embolization post-cath (CVA). Discuss all CP/neuro changes with cath fellow
  - **Radiation injury**: more common in CTO cases. Occurs days to weeks after PCI. Ranges from erythema to skin ulceration
  - **Delayed Hemostasis**: apply indirect pressure (several cm cranial to site of skin access) page gen cards fellow to discuss escalation to cath fellow/vasc surg (see ellucid escalation pathway)

Cardiology — Non-Invasive Cardiac Testing

BASICS

- Non-invasive cardiac testing includes stress/functional and anatomic testing.
- The best approach to testing depends upon: 1) the clinical question being asked, 2) symptom (often chest pain) acuity, 3) baseline CVD risk/known CAD hx, and 4) patient-specific contraindications.

ROLE OF NON-INVASIVE CARDIAC TESTING IN CHEST PAIN EVALUATION



Source: 2021 ACC/AHA Guidelines for Evaluation and Diagnosis of Chest Pain (Circ 2021;144:e368-e454)

Deciding between CCTA (anatomic) and stress imaging in an intermediate-high risk patient:

- CCTA favored: Age<65y, to rule out obstructive CAD, to detect non-obstructive CAD, prior functional study w/o conclusive results, for bypass graft assessment, known anomalous coronaries, parallel evaluation of aorta, pulmonary arteries, or left atrial appendage desired.
- Stress imaging favored: Age>65y, if known >50% (obstructive) CAD to assess for specific areas of ischemia, prior CCTA w/o conclusive results, parallel eval for scar or microvascular dysfunction (PET or CMR).

STRESS/FUNCTIONAL TESTING

- **Indications**:
  - Diagnose CAD: Workup *stable* angina in pts with *intermediate-high risk* of CAD. Consider spectrum of non-invasive tests vs. cath in intermediate-risk pts presenting with more acute sx. Not indicated in pts with no symptoms or at low risk.
  - Evaluate new or changing sx concerning for ischemia in pts with known CAD.
  - Post-revascularization: Evaluate pts with angina or asymptomatic pts if incomplete revasc or >2y post-PCI/5y post-CABG.
  - Pre-op risk assessment: If indicated (see *Perioperative Medicine*).
  - Other: Newly diagnosed HF or cardiomyopathy likely secondary to ischemia, functional capacity (for exercise prescription), viability testing, valvular disorders, dobutamine stress echo in LFLG AS, quantify microvascular disease (PET).
- **Contraindications**: Untreated ACS, MI within 2d, high risk or LM CAD, uncontrolled arrhythmia, ADHF, severe AS or HOCM, recent DVT/PE, acute myo-/peri-/endocarditis, aortic dissection, uncontrolled HTN.
- *Approach to choice of test:* See below for information on choosing a stressor and evaluation modality.
- *Preparation*: NPO 3h prior, longer if imaging or adenosine. Must reverse DNR/DNI for test.
  - If the question is "*Does the patient have CAD?*" → **hold BB and nitrates**
  - If the question is "*How well are meds working in known CAD?*" → **continue BB and nitrates**
  - Hold BB >24h for dobutamine stress test; hold caffeine >12h for adenosine
    - *Positive test results*: Optimize medical rx. Decision re: angiography/revascularization varies by pt (degree of sx, known stenosis, current meds). In ISCHEMIA trial, initial revascularization vs. OMT did not reduce the risk of ischemic CV events for pts with moderate to severe *stable* ischemic heart disease (NEJM 2020;382:1395).
- *Caveats*:
  - Majority of vulnerable plaques are angiographically insignificant (<70% stenosis) → CCTA more sensitive for their detection
  - **Angiographically significant 3VD may produce false-negative vasodilator stress test → "balanced ischemia"**
    - Can see *transient ischemic dilatation* (apparent enlargement of LV cavity during stress) which can occur in 3VD

Approach to choosing a stressor and evaluation modality:

- See Table 5 for full list of **contraindications** by test type (Circ 2021;144:e368-e454).

Choosing a stressor:

- Exercise: Preferred over pharmacologic testing if patient able to reach goal exertion. More relevant to real-world stress.
- Adenosine/Regadenoson:

- *Mechanism*: Vasodilation via cAMP, detect ischemia by coronary steal (stenosed coronary arteries are unable to further dilate, creating a relative perfusion deficit in diseased vessels).
- *Side effects:* Wheezing, bradycardia, HoTN. *Caution if* ACTIVE bronchospasm, high grade AVB, SSS, severe AS
  - Regadenoson (vs adenosine) has decreased respiratory/conduction side effects, is more cost-effective in obese pts, but *caution if* seizure hx (reversal agent aminophylline ↑seizure risk)

- Dobutamine:
  - *Mechanism:* Positive inotropy and chronotropy via β-1 receptor agonism. Extremely high dose (up to 40 mcg/kg/min)
  - *Side effects:* tachyarrhythmias. *Caution if* MI <48h, hx of malignant arrhythmia, severe AS, HOCM, severe HTN, severe PAH, aortic dissection

Choosing an evaluation modality:

- ECG: Only used as stand-alone with exercise, though often still assessed alongside imaging.
- TTE:
  - Can define ischemia severity and risk-stratify. Additional info on hemodynamics/valve disorders
  - *Do not use* in pts with LBBB, V-pacing, or extensive wall motion abnormalities at rest
- Nuclear imaging (PET or SPECT myocardial perfusion imaging):
  - Utilizes a radiotracer to detect areas of ↓perfusion between rest and stress states. Can also measure LV function, transient LV dilatation, myocardial blood flow reserve.
  - More expensive than TTE & high amount of radiation (SPECT > PET)
  - PET more Sn & Sp than SPECT with faster image acquisition. Less widely available & more expensive. Additional uses for imaging in rheumatologic (i.e. cardiac sarcoid) and oncologic contexts (i.e. cardiac myxoma, metastases).
- Cardiac MRI (CMR):
  - Localize ischemia and infarction, assess LV and RV function, determine myocardial viability. Can also detect microvascular dysfunction, and has other uses (see *Anatomic Testing*).

Exercise Tolerance Test (ETT):

- *Approach*: ETT generally refers to exercise + ECG, though can perform imaging eval (TTE, SPECT) with exercise. Exercise ECG has much lower sensitivity than exercise imaging, but is very cheap and available.
- *Protocols*: Bruce (large changes in workload between stages), modified Bruce (for less fit pts → adds stages of lower workload)
- *Assess*: exercise duration, METs, BP/HR response, HR recovery, double product (HR x SBP), Duke Treadmill Score (estimates risk of CAD in pts w/ chest pain undergoing exercise stress testing (Circ 1998;98:1622)).
- *Diagnostic if*: >85% max-predict HR (220-age), peak double product (HRxBP) >20k, HR recovery (HR_{peak} – $HR_{1min\ post\text{-}exercise}$) >12
- Increased probability of ischemia with: ↑ # of leads with STD, ↑ degree of max STD, ↓ METs when ECG changes occur, ventricular ectopy during recovery, increased time to recovery of ECG, failure of SBP to rise with exercise.

Viability testing:

- *Indication*: Determine viability of ischemic myocardium (assess for hibernating tissue) that may be salvaged w/ revascularization.
- *Modalities*: SPECT, PET, TTE, MRI with exercise or pharmacologic stress. Looking for metabolic or contractile reserve.

ANATOMIC TESTING

Coronary CTA (CCTA):

- *Indications*:
  - Evaluate for the presence and extent of CAD. Primarily anatomc info, though offers plaque characterization and CT FFR.
  - Asymptomatic pts: NOT for screening use. Low-risk pts with sx: high NPV (99%) for CAD rule-out (JACC 2008;52:1724). Moderate-risk pts with sx: reasonable for risk stratification (especially after equivocal stress test).
- *Preparation*: Requires cardiac gating (goal HR 60-70, may need to give BB) and respiratory gating (breath hold for 5+ sec).
- *Results*:
  - 2y ACS risk significantly elevated if high-risk plaque (16%) and/or stenotic disease (6%) (JACC 2015;28:337)
  - Higher Sn & Sp for coronary stenosis compared to cMRI (Annals 2010;152:167)
- Caveats: Less useful in pts with extensive calcifications (older) or stented vessels due to "blooming" artifact (cannot eval patency).

Coronary Artery Calcium (CAC) Scan:

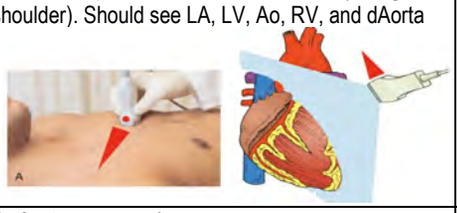
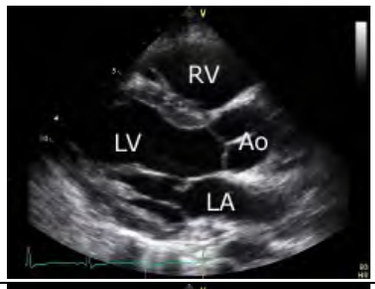
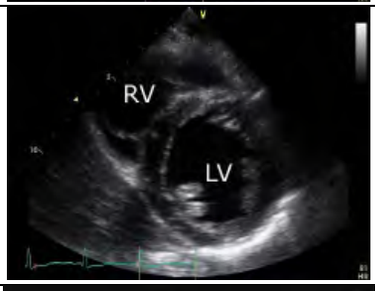
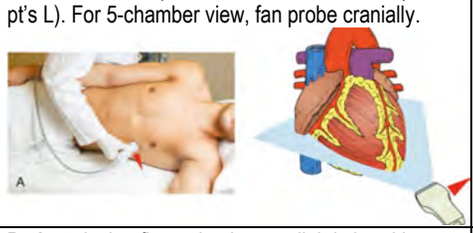
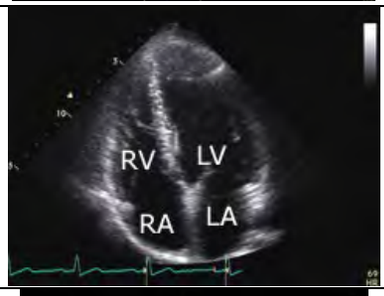
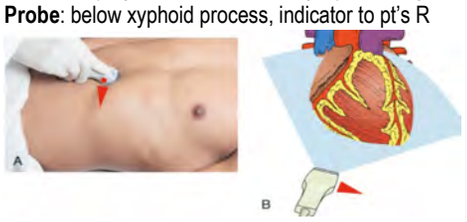
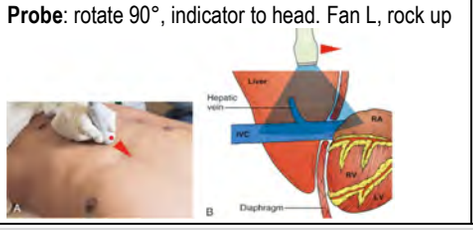
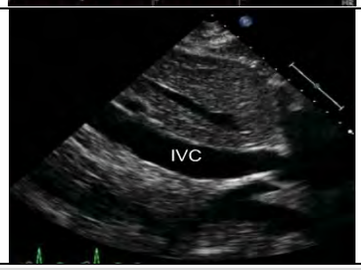
- *Indications*:
  - Risk-assessment (CAC or Agatston) score for ASCVD risk stratification. Used to guide decision-making for primary prevention/statin therapy in asymptomatic pts, ≥40y at intermediate-risk (7.5-19.9% 10y ASCVD risk). Do NOT use as a stand-alone test in eval of sx of myocardial ischemia. Do NOT use in high-risk pts, including those with familial hypercholesterolemia
- *Preparation*: Non-gated, non-contrast (if done independent of CCTA) CT scan.
- *Results*: MESA score accounts for CAC score and is able to refine 10 year risk estimates
  - If CAC score 0 and pt without significant risk factors, reasonable to defer statin therapy for up to 5 years (Circ 2019;140:496).
  - If CAC score ≥100 or >75%ile for age & gender, independent of ASCVD risk recommend aggressive lifestyle changes, ASCVD RF modification (BP, smoking cessation, diabetes treatment), & statin therapy (JACC 2019;73:285)

Cardiac MRI:

- Can be used in a stress test/ischemia eval, also is modality of choice for assessment of funtional & tissue properties of the heart that cannot be adequately assessed with TTE or CCTA (inflammation, scarring, infiltration, cardiac tumors, pericardial disease)

Cardiology

Echocardiography

View/Description	Position	View*
PARASTERNAL LONG AXIS • LV size, function, wall thickness (septum/posterior wall) • MV/AoV function/flow (w/ Doppler) • LVOT diameter, aortic root size	**Patient**: lying on left side, with left arm under head **Probe**: 2-3 inches left of sternum at 3rd-4th intercostal space, indicator at 10 o'clock (facing R shoulder). Should see LA, LV, Ao, RV, and dAorta 	
PARASTERNAL SHORT AXIS • Cross-sectional views of the heart from base to apex, at level of AoV, MV and mid-ventricle/papillary muscles	**Patient**: same as above **Probe**: from long axis view, rotate probe clockwise until indicator at 2 o'clock (facing L shoulder). Fan probe to L hip until at level of papillary muscles. 	
APICAL 4 CHAMBER • RV/LV size, function, thrombus • TV/MV function/flow (w/ Doppler) • Septal size/motion • Pericardial effusion • In 5-chamber view, can see AoV and proximal ascending aorta	**Patient**: lying flat on back or left decubitus **Probe**: at PMI w/ probe indicator at 3 o'clock (to the pt's L). For 5-chamber view, fan probe cranially. 	
SUBXIPHOID (aka subcostal) • RV/LV size, function • Pericardial effusion	**Patient**: laying flat on back, can slightly bend legs **Probe**: below xyphoid process, indicator to pt's R 	
INFERIOR VENA CAVA • IVC diameter and respiratory variation gives estimate of volume status and RA pressure • Most helpful for extremes of volume status measurement (i.e. very dry or very wet) *Images from: Soni, N. J., Arntfield, R., & Kory, P. (2020). *Point of care ultrasound*. Elsevier.	**Patient**: same as above **Probe**: rotate 90°, indicator to head. Fan L, rock up 	

REVIEWING THE MGH REPORT: for questions or clarification of findings, call Echo Lab (**x6-8871**) or page on-call Echo Fellow

- Valvulopathy: stenosis/regurgitation (valve area, gradients, severity), leaflets, vegetations
- Structure/chamber dimensions: aorta, LVIDd & LVIDs (LV internal diameter in diastole, range: 42 – 58mm & systole, range: 25 – 40mm), IVS (septum, 6-10mm), PWT (posterior wall thickness, 6-10mm, ↑ in LVH, diastolic dysfunction), LV volume (ULN: 74ml/m^2 in men 61 in women, <40 suggest restrictive), LA volume (ULN: 34ml/m^2, ↑in MR/MS, diastolic dysfunction, AF)
- EF: "preserved" EF ≥50%, "borderline" EF 40-50%, "reduced" EF <40%
- WMA: territory correlates w/ coronary vessels (anterior + septal = LAD, inferior = RCA, lateral = LCx). If global WMA, r/o diffuse ischemia vs non-ischemic insult (sepsis, stress)
- RVSP: RVSP=4v^2 + RAP. **RAP assumed to be 10 mmHg** and v = TR jet velocity. RVSP >35mmHg (<60yrs) and >40mmHg (> 60yrs) is elevated.
- Shunt detection: agitated saline contrast study (i.e. TTE w/ bubble) to detect PFOs, ASDs, and pulmonary arteriovenous shunts

Indications for STAT TTE:
- Eval hemodynamic instability of suspected cardiac etiology
- Eval for early MI complication
- Suspected MI w/ non-diagnostic biomarkers and EKG
- Identify cause of cardiac arrest

CLINICAL QUESTIONS AND ASSOCIATED TTE FINDINGS

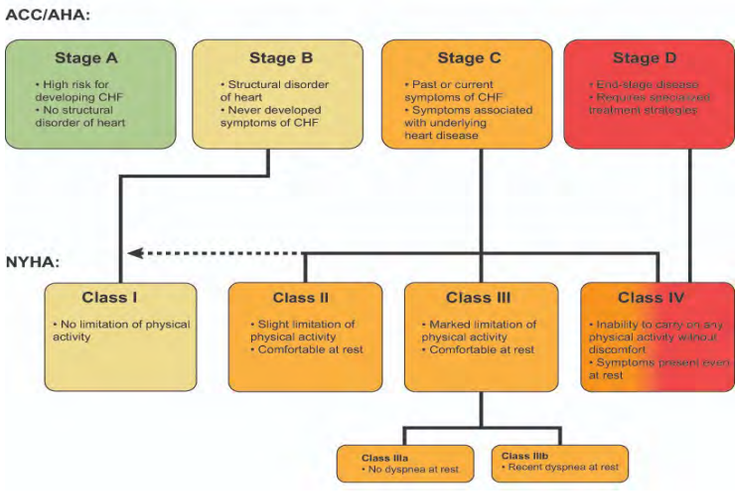
- Right heart strain in acute PE: RV WMA or hypokinesis, RV dilation (RV:LV ratio >1), interventricular septal bowing, IVC collapse, "D-sign": septal flattening, "McConnell's sign": RV free wall akinesia w/ normal RV apex motion (77% Sn, 94% Sp for acute PE)
- Tamponade: large effusion, swinging heart, R-sided chamber collapse, interventricular septal bowing, dilated IVC (no ↓ w/ inspiration)
- ACS/mechanical complications of ACS: regional WMA, septal/free wall rupture, acute MR, LV thrombus
- Stress (Takotsubo) cardiomyopathy: LV apical ballooning and akinesis/hypokinesis; Heart failure: depressed EF, RV/LV hypertrophy and/or dilation
- Diastolic dysfunction: LA enlargement, E/e' >14, LVH (note: diastolic dysfunction not typically called on MGH TTE reports)
- Constrictive pericarditis: thickened or hyperechoic pericardium, abnormal septal motion, respiratory variation in ventricular size, dilated IVC
- Cardiac amyloid: biatrial enlargement, increased LV and RV wall thickening, valvular thickening, diastolic dysfunction, paradoxical LFLG AS

Cardiology

Heart Failure

Initial Workup - New Heart Failure Diagnosis

- **Clinical syndrome** with signs/symptoms consistent with impaired cardiac function ± cardiomyopathy
- Echocardiography: TTE for all new presentations; obtain thereafter only if concern for clinical/functional change
  - **HFrEF** (EF ≤40%), **HFmrEF** ("mid-range" EF 41-49%), **HFpEF** (EF ≥50%), **HFrecEF** ("recovered")
- Ischemic workup: FHx, ECG, TnT, noninvasive or invasive cardiac testing
- Non-ischemic workup: FHx, genetic testing, med hx, alcohol use history, lipid panel, TSH, A1c, urine hCG, iron studies, HIV, SPEP/SFLC w/ UFLC
  - *Consider*: cardiac MRI/PET, ANA, *T. cruzi* serologies, viral panel, antimyosin Ab, tox screen, thiamine/carnitine/selenium, genetic testing, ARVC, sarcoid, PYP scan/bone scintigraphy (amyloid), cardiac masses; endomyocardial bx (if serologic testing neg, new onset <6mo unexplained HF, unexplained HF <2wks and HDUS, major arrhythmias) to r/o myocarditis
- Consider high-output etiologies: anemia, thyroid dysfxn, liver failure, Paget's, systemic infection, AV shunts


ACC/AHA:
Stage A
• High risk for developing CHF
• No structural disorder of heart
Stage B
• Structural disorder of heart
• Never developed symptoms of CHF
Stage C
• Past or current symptoms of CHF
• Symptoms associated with underlying heart disease
Stage D
• End-stage disease
• Requires specialized treatment strategies
NYHA:
Class I
• No limitation of physical activity
Class II
• Slight limitation of physical activity
• Comfortable at rest
Class III
• Marked limitation of physical activity
• Comfortable at rest
Class IV
• Inability to carry on any physical activity w/o discomfort
• Symptoms present even at rest
Class IIIa
• No dyspnea at rest
Class IIIb
• Recent dyspnea at rest

Dilated Cardiomyopathy

Etiologies: **ischemic** (most common cause, 50-75%), HTN/LVH, valvular (e.g. MR), myocarditis, stress-induced (Takotsubo), tachyarrhythmia, infiltrative (as below), CTD, ARVC, LVNC (left ventricular non-compaction), HIV, cocaine/methamphetamines, EtOH, chemotherapy, nutritional deficiency, cirrhosis, sepsis, peripartum, idiopathic/genetic

Condition	Etiology and Management
Alcohol-induced	Mechanism: associated with >80g/d EtOH (6 standard drinks) over >5y (toxic to myocytes via O_2 free radicals + defects in protein synthesis) Tx: abstinence + HF therapy Prognosis: better/equivalent to idiopathic CM if <20g/d (<2 drinks) or abstinence, worse w/ continued EtOH use
Stress-induced (Takotsubo) (JACC. 2018;72:1955)	Mechanisms: catecholamine surge from physical/emotional stress, coronary artery spasm, microvascular ACS Presentation: may present like ACS with CP (most common), SOB, shock, syncope. If in shock, urgent TTE to assess for LVOT obstruction Dx (need all 4): **1)** transient dysfxn of LV mid-segments, WMAs extending beyond a single coronary distribution; **2)** rule out ACS/obstructive CAD (via cath); **3)** new ECG Δ (STE or TWI) OR ↑TnT; **4)** absence of pheo or myocarditis Tx/Prognosis: remove stressor, **ACEi** (may improve survival), BB; most recover LV function in 1-4w

Hypertrophic Cardiomyopathy (HCM) (Circulation 2024 ;149)

Characteristics: LV and/or RV hypertrophy of various morphologies ± LVOT dynamic obstruction (**HOCM**), diastolic dysfxn, ischemia, MR; **risk of arrhythmia/SCD**

Exam: SEM at LLSB/apex that augments with Valsalva or on standing (due to ↓preload); S2 paradox split, S4

Dx: **ECG** (prominent voltages w/ depolarization abnormalities, large abnormal Q waves in inferior/lateral leads, LAD, giant negative T waves in V2-V4 (apical HCM variant aka "Yamaguchi syndrome")), **TTE** (unexplained LVH >15mm, SAM of MV, outflow tract gradient +/- provocative testing), **cMRI** (late gadolinium enhancement [LGE] = fibrosis)

Clinical **genetic testing** (mutation in ~70%) helpful for family screening; not useful for dx or risk stratification

Tx: **avoid volume depletion** or high dose vasodilators (may worsen obstruction); **phenylephrine is pressor of choice** if no response to IVF bolus for HoTN (↑afterload, stents open LVOT). Activity restriction, meds (BB > verapamil). Consider mavacamten if LVEF ≥ 55% (VALOR-HCM); septal ablation or surgical myectomy for medically refractory sx, ICD (for high SCD risk, see below)

Risk factors for **SCD/VT**: prior VT/SCD/unexplained syncope; FHx of SCD in 1° relative; massive LVH (>30mm); NSVT on Holter; abnormal BP response to exercise; burden of LGE on cMRI; h/o suspected cardiac syncope; EF<50%

Restrictive Cardiomyopathy (JACC 2010;55:1769) – *conditions below may also manifest as Dilated CM*

Etiologies: in addition to below, Löffler's, radiation, metabolic storage disease, carcinoid

Tx: treat underlying disease and HF as below. For **amyloidosis**: tafamidis (↓TTR deposition) (NEJM 2018;379:1007)

Condition	Presentation	ECG	Echo	cMRI
Amyloidosis (AL, TTR)	- HF w/ other findings of **amyloid** (renal, neurologic, hepatic dz)	- **↓voltage,** pseudoinfarct pattern in inferolateral leads	- Symmetric LV/RV **↑wall thickness,** speckled myocardium	- LGE in subendocardium
Hemochromatosis	- If hereditary: M >30yo; F >40yo - If 2°: any age - Abnl **LFTs**, arthralgias, **DM**, **hyperpigmented** skin	- **SVT** (ventricular conduction abnormalities rare)	- Dilated LV with global systolic dysfunction	- Iron overload with T2 protocol
Sarcoidosis	- **Young** adult w/ HF *(more commonly as DCM)*	- **Infrahisian block**, atypical infarct pattern	- Variable wall thickness, focal/global hypokinesis, LV aneurysm	- Patchy enhancement of basal and LV walls

Christian Andersen

INPATIENT ACUTE DECOMPENSATED HEART FAILURE (ADHF)

- Admission orders: **tele**, **2g Na** restricted diet, daily **standing weights**, **strict I/Os**, DVT ppx
- SDU Admission: EF <25%, NTproBNP ≥ 2,500, arrhythmia-induced HF. Black & Latinx pts w/ HF are less likely to be admitted to cardiology services, contributing to racial inequities in HF outcomes (Circ Heart Fail 2019;12:e006214).
- **Avoid**: **CCB** (esp. **non-dihydropyridines**), **NSAIDs**, **flecainide**
- Check **NT-proBNP** (& **weight**) on **admission** and at **discharge**
  - ADHF unlikely if NT-proBNP <300 (NPV 98%), likely if >450 (>900 if age >50) (Am J Cardiol 2005;95;948)
  - Difficult to interpret in CKD/dialysis. May be falsely low in **obesity**, **HFpEF**
- Screen for & treat **iron deficiency** in all HF pts independent of Hgb (JACC HF 2019;7:36)
  - Dx: ferritin <100 or ferritin <300 + TSat <20% (JACC 2017;70:776); though some evidence that TSat ≤19.8% or serum iron ≤13μmol/L most predictive & ferritin may be less useful (Circ Heart Fail 2018;11:e004519)
  - Tx: replete with IV iron (JACC 2018;71:782) to ↓sx, ↑functional capacity, ↑QOL (FAIR-HF, NEJM 2009;361:2436); PO ineffective in HF (JAMA 2017;317:1958)

ADHF MANAGEMENT – FLOOR/SDU

1. Identify **hemodynamic profile** & **triage** accordingly (JACC 2019;74:1966)
   - Warm vs Cold: adequate vs inadequate tissue perfusion (AMS, lactate, cool extremities, narrow PP)
   - Dry vs Wet: presence vs absence of congestion (JVD, crackles, pleural effusions, ascites, LE edema, interstitial/alveolar edema on CXR)
   - Evaluate for signs of **pulmonary congestion on exam**. Pulm edema may be **absent on CXR** in chronic HF due to lymphatic compensation (Chest 2004;125:669)

		Congestion at Rest (PCWP)	
		Yes	**No**
Low Perfusion at Rest? (CO)	**Yes**	Warm & Dry (Compensated) *Outpatient mgmt.*	Warm & Wet (Congested) *Diuresis ± Vasodilators*
	No	Cold & Dry (Low Flow State) *Inotropes, vasodilators*	Cold & Wet (Decompensated) *Tailored Therapy (ICU)*

   - ~80% of decomp HFrEF and nearly all decomp HFpEF pts will be warm and wet
2. **History**
   - **Identify precipitants**: dietary/med non-adherence (~40%), **new ischemia/infarction**, uncontrolled HTN, arrhythmia, inadequate diuretic dose, meds (NSAIDs, steroids, CCB, TZDs, anthracyclines), acute infection (URI, PNA, UTI), AKI, PE, toxins (EtOH, cocaine), new/worsening valve disease, myocarditis
   - **Cardiac/HF history** (last EF, dry weight, prior ischemic w/u, prior TTE, cardiologist); accurate PAML; social history
3. **Early/Acute Management**:
   - **Diuresis**: ↓CVP, PCWP to optimize Starling curve mechanics & relieve sx (NEJM 2017;377:1964; JACC 2020;75:1178)
     - Initial tx: IV loop (furosemide, torsemide, bumetanide), start w/ 2-2.5x home dose (IV/PO). No difference b/w continuous gtt vs bolus (NEJM 2011;364:797); furosemide & torsemide have same outcomes (JAMA 2023;329:214-223). See *Advanced Diuresis*
     - Refractory diuresis: metolazone 2.5-5mg (or chlorothiazide 500mg IV) administered 30min before loop diuretic. May need RHC to clarify hemodynamics or inotropes to augment diuresis. Acetazolamide (500mg daily) may also augment successful decongestion (NEJM 2022;387:1185). Step-up pharmacologic therapy superior to RRT in the setting of cardiorenal syndrome (NEJM 2012;367:2296)
     - Worsening renal function: occurs in ~23% of pts treated for ADHF. Mild-mod "Cr bumps" are likely benign hemodynamic changes, should not necessarily preclude further diuresis if pt still congested (Circ 2018;137:2016)
     - Endpoints: target resolution of signs/symptoms of congestion. Daily weights & hemoconcentration are useful adjuncts
   - If acute pulmonary edema, **NIPPV** may improve mortality and reduce need for intubation (Annals 2010;152:590)
   - **Vasodilators**: arterial/venous dilation can relieve symptoms by ↓afterload, ↓PCWP and ↑SV. Can acclerate early sx relief. Consider esp. in severe HTN, acute MR, acute AR
     - Floor: isosorbide dinitrate, hydralazine, nitropaste, captopril; SDU/CCU: nitro gtt, nitroprusside gtt
   - **Guideline-Directed Medical Therapy (GDMT)**: if not in cardiogenic shock or new AKI, continue ACEi/ARB/ARNi and βB during ADHF (but do not newly initiate βB) (EHJ 2009;30:2186)
4. **Pre-Discharge Optimization**: Document **d/c weight** & **NT-proBNP,** appt in HF Transitions Clinic
   - **HFrEF (EF ≤40%) GDMT, including HFrecEF (recovered EF),** prioritize initiation of low-dose quadruple therapy prior to d/c:
     - **Beta blockers**: initiate, uptitrate evidence-based βB (carvedilol, metoprolol succ., bisoprolol) (COPERNICUS; MERIT-HF). Caution if recently weaned from inotropes
     - **RAAS inhibitors**: if renal fxn stable, initiate/titrate ARNI (sacubitril/valsartan) (PARADIGM-HF; PIONEER-HF), second line ACEi/ARB (CONSENSUS; CHARM). Switch to ARNI from ACEi/ARB if no contraindications/cost concerns, 36h washout period for ACEi prior to starting ARNI.
       - Guidance for GDMT in advanced CKD: JACC HF 2019;7:371
     - **Mineralocorticoid receptor antagonist**: initiate spironolactone or eplerenone if CrCl>30 (EMPHASIS-HF; RALES). Watch for rebound hyperK after de-escalation of diuretics (check K, Cr within 72h of discharge)
     - **SGLT2i (dapaglifozin, empagliflozin)**: further reduce CV mortality & HF admissions regardless of DM (DAPA-HF; EMPEROR-Reduced; EMPULSE; Lancet 2020;396:819 (see *Outpatient Type 2 Diabetes*)
     - **GDMT dosing - AHA/ACC/HFSA 2022 Guidelines** (Circ 2022;145:895)

	βB		**ARNi/ACEi/ARB**			**MRA**		**SGLT2i**	
	metop succ	carvedilol	sacub/val	lisinopril	losartan	spirono	epler	dapag	empag
Initial Dose (mg)	12.5-25 qD	3.125 BID	49/51 BID	2.5-5 qD	25-50 qD	12.5-25 qD	25 qD	10 qD	10 qD
Target Dose (mg)	200 qD	25-50 BID	97/103 BID	20-40 qD	50-150 qD	25-50 qD	50 qD	10 qD	10 qD

- **Diuretic plan**: determine maintenance diuretic dose and provide specific instructions for taking additional rescue doses. Observe on maintenance dose and decide if needs K replacement
- **HFmrEF** (EF 40-49%): treat with diuretics & consider adding GDMT agents for HFrEF (Curr Heart Fail Rep 2020;17:1)
- **HFpEF** (EF ≥50%): prevent volume overload, treat with diuretics, treat comorbidities (DM, HTN, AF)
  - **SGLT2i** only agent found to ↓CV death/hospitalizations in pt with EF ≥40% (EMPEROR-Preserved)
  - Consider **spironolactone** if normal renal fxn/K, ↓CV death/admits in N/S Am. sites in TOPCAT (Circ 2015;131:34)
  - No proven benefit to BB (EHJ 2018;39:26), ACEi (PEP-CHF), ARNi (PARAGON-HF), ARB (CHARM-Preserved; I-PRESERVE)
- ICD indicated if: ischemic CM w/ EF ≤30 or ≤35% w/ NYHA II-III; CRT if: EF ≤35% & prolonged QRS ± LBBB & some w/ EF ≤50% (see *Cardiac Devices: PPM/ICD* & guidelines for specifics: JACC 2013;61:e6; EHJ 2016;37:2129)

Outpatient Heart Failure (JACC 2021;77:772, Circ 2022;145:895)

Not comprehensive; assumes EF ≤ 40% (HFrEF), co-management by cardiology and/or heart failure specialist.

- At each visit: assess med/dietary/lifestyle compliance, document weight, detailed volume exam, assess symptoms and classify ACC Stage/NYHA Class, review current GDMT, review ambulatory BP / HR measurements for GDMT titration targets
- Lab monitoring: BMP/Mg and 1-2 weeks following uptitration of ACE-i/ARB/ARNi; spironolactone requires close monitoring
- Goal: toleration of target doses of ACE/ARB/ARNI, β-blocker, aldosterone antagonist, and SGLT-2 inhibitor without symptomatic hypotension or metabolic disarray. For β blockade, target resting HR < 70 without postural hypotension or unacceptable SE.
- Principles: start GDMT immediately on dx, often "quad therapy" at lower than target dosing is preferred over maxing out a single agent
- Diuretic: see *Advanced Diuresis.* Diuretic needs may change when SGLT-2i is added due to mild diuretic effect.
- Avoid: NSAIDs, CCBs, flecainide, steroids, OTC decongestants (e.g. Sudafed), Bactrim
- Special considerations/scenarios:
  - Ivabradine: add if sinus rhythm & resting HR > 70 on max β blockade. Start at 2.5 mg – 5 mg qd
  - Hydralazine/isosorbide dinitrate: add if SBP persistently > 130 on target GDMT; especially beneficial in AA patients
  - Symptomatic hypotension on GDMT: consider over-diuresis or other offending prior to reducing GDMT
- Adjuvant care/ambulatory referrals to consider: cardiac rehab (often under-prescribed); nutrition consultation for assistance with dietary adherence; patient-centered education is critical to enhance adherence

Cardiogenic Shock – CCU

- Definition: HoTN (**SBP<90** for 30min or pressor req) + **hypoperfusion** (cold extremities, oliguria, lactate) + hemodynamics (**CI <2.2, PCWP >15**) (EHJ 2019;40:2671)
- Etiology: acute MI ± mechanical complications, end-stage heart failure, acute myocarditis, acute MR/AR, myocardial contusion
- Evaluation: ECG, troponin to r/o acute MI. TTE to exclude tamponade/mechanical lesions/contraindications to MCS
- Monitoring: A-line, consider **PA catheter** for inotropes/pressors and MVO_2 monitoring

Immediate Management:

- If c/f **acute MI**, activate cath lab for PCI (only intervention proven to improve outcomes in cardiogenic shock) (NEJM 1999;341:625)
- Consider early **SHOCK consult** (p11511). Escalating inotropes/pressors exacerbate myocardial supply/demand imbalance and are associated with poor outcomes. Emerging evidence supports early initiation of MCS (Cath Cardio Interv 2019;93:1173)
- Stabilize MAP with **norepinephrine** PRN prior to obtaining PA catheter to guide tailored therapy

Tailored Therapy: uses invasive hemodynamic monitoring (i.e., PAC) to guide medical therapy

- **Goals**: tissue perfusion (↑CO, MAP), decongestion (↓CVP, PCWP), ventricular unloading (minimize myocardial O_2 demand)
  - **Preload**: LVEDV ∝ LVEDP ≈ PCWP; goal **PCWP 14-18, PAD 16-20, CVP 8-12** → diuresis, UF with RRT, TNG
- **Afterload**: wall stress ∝ MAP (Laplace's law); SVR = (MAP - CVP)/CO; goal **MAP >60, SVR <800-1200**
  - Vasodilators: captopril, hydralazine, nitroprusside, TNG, isosorbide dinitrate
  - Vasopressors: ↑afterload, sometimes needed to ↑MAP in mixed shock or to counteract vasodilatory effect of inodilators
  - IABP: see *Mechanical Circulatory Support*
- **Contractility**: ∝ CO for given preload/afterload; goal **CO>4, CI >2.0-2.2, MVO_2 >65**
  - **Dobutamine** (inodilator): β1>β2 agonist (↑production of cAMP); initial dose 0.5-1 mcg/kg/min
    - Watch for tachycardia, ↑ventricular response to AF, arrhythmias, ischemia, HoTN, tachyphylaxis in infusions >24-48h
  - **Milrinone** (inodilator): PDE-3 inhibitor (↓breakdown of cAMP); initial dose 0.125 mcg/kg/min
    - Watch for tachycardia, arrhythmias, ischemia, HoTN. Compared to dobutamine, milrinone has longer half-life, greater pulmonary vasodilatation, slightly less chronotropy
    - Preferred in patients on βB and w/ RV failure. Renally cleared. Often choice for home inotrope for palliative therapy
  - Epinephrine, norepinephrine, dopamine (inopressors): use if severe HoTN often in combination with inodilators
    - Watch for tachycardia, arrhythmias, end-organ hypoperfusion
- **Advanced**: consideration of need for mechanical circulatory support or transplant
  - Goal of mechanical circulatory support: improve systemic perfusion while reducing myocardial oxygen demand (in contrast to inotropes which ↑CO at the expense of increased oxygen demand); see *MCS*
- **Limitations**:
  - **CO** approximated via thermodilution or Fick equation: CO = VO_2/(13.4 x Hgb x [SpO2-MVO_2]); CI = CO/BSA; VO_2 = 125 x BSA
    - Thermodilution: uses temp gradient between two points on PAC. Less reliable if shunt/valvular insufficiency (e.g., TR)
    - Fick equation: assumes a VO_2 (oxygen consumption) that in reality varies depending on physiologic state (e.g., infxn)

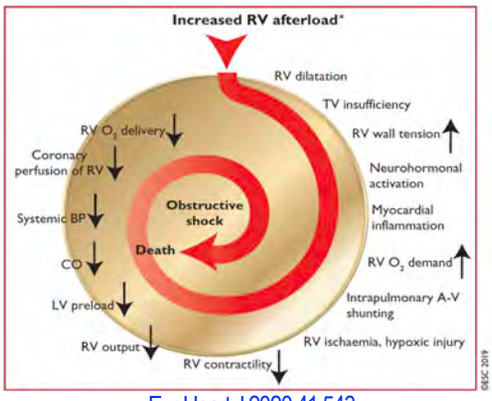
Cardiology

Right Ventricular Failure

Pathophysiology

- Normal RV function: governed by systemic venous return, PA pressure, pericardial compliance, and native contractility of the RV free wall and interventricular septum (where RV and LV are "tethered").
  - The RV is coupled to the high-compliance, low-resistance pulm circulation → RV ejects blood at lower pressure compared to LV → RV is more afterload sensitive than LV. RV can adapt to changes in volume > pressure.
- Acute RV Failure: RV & LV interdependent → failure of RV → failure of LV via: (1) decreased LV preload, as RV output = LV preload & (2) septal bowing into LV, causing diastolic impairment ("Diastolic Ventricular Interaction")
  - ↑RV afterload (e.g. PE, hypoxia, acidemia), ↑RV preload (e.g. L→R shunt or TV disease), or ↓RV contractility (e.g. MI, myocarditis) all lead to increased RV wall stress & resultant ischemia
- Chronic RV Failure: gradual ↑RV afterload (from Pulmonary Hypertension / Pulmonic Stenosis / Tricuspid Regurgitation)→ **RV "death spiral"**

RV "death spiral"



Eur Heart J 2020;41:543

Clinical Features and Workup (Circ 2018;137:e578-e622)

- Exam: ↑JVP, peripheral edema, RV heave, pulsatile liver, split S2, new TR (holosytolic murmur at LLSB with radiation to RLSB)
- Imaging: PA/lateral CXR; CT → RV/LV ratio >0.9 suggests RV strain
- Echo: measure RV size/function to elucidate underlying etiology. RVEF based on displacement of base towards apex; TAPSE = tricuspid annular plane systolic excursion (normal ≥ 17 mm; reflects RV apex-to-base shortening, correlates with RVEF)
  - RVSP: correlates w/ RHC but can vary up to 10mmHg (esp w/ chronic lung disease, PPV)
- RHC w/ placement of PA line: gold standard for measurement of ventricular filling pressures, CO, PA pressures
  - RV function: CVP/PCWP ratio: normal = 0.5; ↑ is sign of RV failure; PAPi: (PAs – PAd)/CVP <0.9 = RV failure, for pts w/ VAD < 1.85 = RV failure; RV stroke work index: (mPAP – CVP) x (CI/HR) x 0.0136 (normal 8-12 g/m/beat/m^2)
- Labs: ↑NT-proBNP, troponin, also ↑Cr and LFTs secondary to venous congestion

Management (AHA: Circ 2018;137:e578)

- Treat reversible causes (pericardial disease, RVMI, PE, hypoxemia, infections)
- Preload (CVP goal 8-12mmHg): both hypo- and hypervolemia can ↓CO
  - Volume Depletion (PE, Tamponade, RVMI): judicious IVF (0.5-1L) in absence of CVP elevation (goal CVP 10-14 in RVMI)
  - Volume Overload: IV diuresis to ↓RV filling pressures, ↓functional TR, and improve LV CO; consider UF/CVVH if refractory to IV diuresis
- Afterload:
  - Systemic: if pt hypotensive, start pressors – **do not tolerate HoTN** as propagates RV death spiral (↓CPP); Goal MAP>65 & MAP>mPAP (EHJ Acute CV Care 2022;11:77) no clinical data regarding pressor of choice, but often choose vasopressin or norepinephrine (vaso affects PVR less than norepi) (Crit Care Med 2007;35:2037)
  - Pulmonary: remove factors that ↑pulm vasc tone (e.g. hypoxemia, acidemia). Consider pulm vasodilators if evidence of PAH (inhaled>oral to deliver vasodilators to ventilated vascular beds)
    - Types: iNO, prostacyclin agonists (epoprostenol (Veletri), inhaled or IV), endothelin antagonists (e.g. bosentan, ambrisentan), nitric oxide enhancers (e.g. PDE-5 inhibitors: sildenafil, tadalafil)
- Contractility: dobutamine or milrinone; milrinone: ↓RV afterload by pulmonary vasodilation but ↑risk of hypotension; epinephrine ↑ RV contractility and ↑MAP
- Devices: if refractory RVF, consider RV MCS and/or biventricular support (ProtekDuo, Impella RP, VA-ECMO)

Intubation and Mechanical Ventilation (Curr Heart Fail Rep 2012;9:228)

- RV preload is "extrathoracic" and afterload is "intrathoracic" → intubation & positive pressure ventilation ↑ pulmonary vascular resistance (PVR) and ↑ RV afterload → ↑ RV dilation → "death spiral"
- IMV/NIPPV in RV failure precipitate risk for **hemodynamic collapse** & **cardiac arrest;** trial of HFNC for hypoxemic respiratory failure preferred prior to IMV/NIPPV given minimal effect on RV afterload.
  - Drugs commonly used in intubation (BZDs, propofol, muscle relaxants) → tendency towards vasodilation and negative inotropy → decreased venous return → decreased LV preload → systemic hypoTN → propagates "death spiral"
  - Consider **RSI w/ hemodynamically stable induction agents** (ketamine/etomidate >> propofol for induction) & push dose epinephrine (5-20mcg) or phenylephrine if emergent intubation; have norepinephrine in line **anticipating hypotension.**
- Vent management: prevent hypoxemia & hypercarbia (↑PVR), consider moderate TV (~8cc/kg), low PEEP (<8 cm H_2O), and moderate plateau pressure goal (<30 mmHg) to help minimize RV afterload

Right Ventricular Myocardial Infarction (ACC/AHA: Circ 2013;127:e362)

- EKG: check R-sided ECG leads in pts with inferior STEMI (10-15% have RV involvement)
  - 1mm STE in V4R → 88% Sn, 78% Sp in inferior STEMI; STE III>II suggests RCA > LCx and RVMI
  - High-grade AV block seen in ~50% of pts with RVMI
- Management: pts with RVMI may initially benefit from fluid bolus; **caution** w/ **TNG** (↓preload) & **BB**

Cardiology

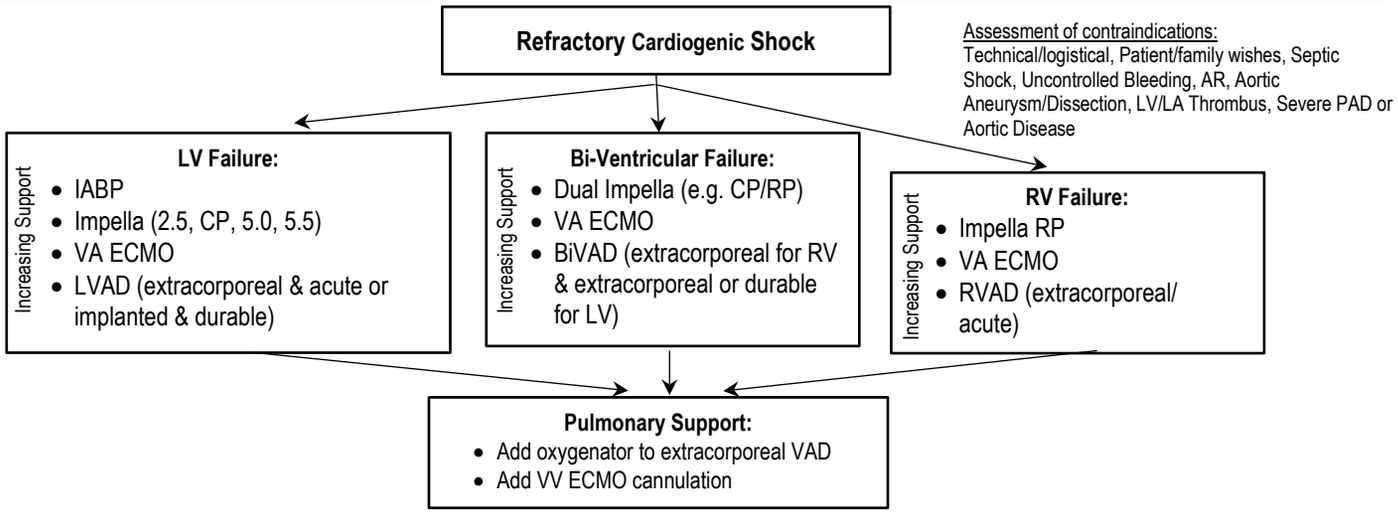
Mechanical Circulatory Support

MECHANICAL CIRCULATORY SUPPORT (MCS) (JACC HF 2020; 8(11):879 ; Heart Int 2022; 16(1):37)

Note: if inotrope-refractory cardiogenic shock, call SHOCK team (p11511) and/or HCICU attending (p29151). VAD Coordinator (p11045).

Selected MCS Modalities

Device	Indications	Support Provided	Considerations	Management	Complications
IABP (intra-aortic balloon bump)	- Refractory heart failure (**bridge** to durable MCS or transplant, bridge-to-bridge) - Refractory ischemia - **Cardiogenic shock**/massive PE - Refractory malignant **arrhythmias** - Support during **high-risk procedures**: o Complex PCI o Ablation of ventricular arrhythmias o Percutaneous valve repair - Acute allograft failure	Mechanism: balloon inflation/deflation; **LV support** Minimal hemodynamic support (**0.5 L/min**), greater in ADHF than acute MI shock (Am J Card 2019;124:1947) - **↓LV afterload (deflation)**- improves forward flow in MR/VSD - **↑Coronary perfusion (inflation)** - Requires native contractility & stable rhythm	- Bedside insertion (quick) - Does not always require AC (when at 1:1) - No ↓mortality in cardiogenic shock (IABP-SHOCK II, NEJM 2012;367:1287) - Prevents mobility (if femoral placement) - Least costly	- Check **CXR** daily (tip 1-4cm below aortic knob) - Check **waveform** twice daily - Wean by ↓ ratio (then return to 1:1, stop AC, pull) - Pulse checks	- **Limb ischemia** - Vascular injury - Thromboembolism - Bleeding - Infection - Balloon leak/rupture (STAT c/s to attending and vascular surg c/s)
Impella		Mechanism: axial flow continuous pump **Partial LV support (LV->Aorta)** - Cath lab (percutaneous) placement: Impella 2.5 (**2.5 L/min**), Impella CP (**3.5 L/min**) - OR placement: Impella 5.0 (**5 L/min**) or 5.5 (**6.5 L/min**) **Partial RV support (VC->PA)** - Impella **RP (>4 L/min**)	- Ventricular unloading - **Requires AC** (purge ± systemic) - Allows pt **mobilization** (if axillary placement) - Longer-term support (days to weeks) - ↑complications comp ared to IABP - May ↓ major adverse cardiac events, not mortality (PROTECT II, Circ 2012; 126:1717–1727)	- P1 (lowest) to P9 (highest support) - Check urine color (**hemolysis**), LDH - Check **suction events** (↓preload, RV failure, position) - Check ventricular arrhythmias (device migration)	- Infection - Bleeding - Limb ischemia - Thromboembolism - Thrombocytopenia - Vascular injury - **Position alarm** (reposition under fluoro/echo)
VA-ECMO		**Full bi-ventricular support** (**4-10 L/min**) + oxygenation & CO2 clearance	- Bedside and urgent insertion possible - Short-term support (days/weeks) - Often requires Impella for LV venting (prevent complications such as pulmonary edema)	See *ECMO*	
Durable VAD	- **Bridge to transplant** - **Bridge to candidacy** - **Destination therapy** - Bridge to **recovery** (LV unloading can be therapeutic)	**Full LV support** (**10 L/min**) - HeartMate II - HeartMate 3 - HeartWare HVAD 48% reduction in all cause mortality with LVAD as compared to optimal GDMT in Class IV HF (REMATCH) Off-label for RV support (RVAD) or both (BiVAD)	- **Mobility** - **Long-term support** (years) - **Require lifelong anticoagulation**	- **BP via manual cuff w/ doppler** (goal MAP 70-80); continuous flow device does not generate pulse - If hypotensive: A-line - If unconscious, w/o hum and unable to troubleshoot OR MAP<50: chest compressions - TTE if any concern	- **Acquired vWF deficiency** - **Bleeding** - **Hemolysis** (possible pump thrombosis) - Ventricular arrhythmias - Thromboembolism - RV failure - AR - **Driveline infections**

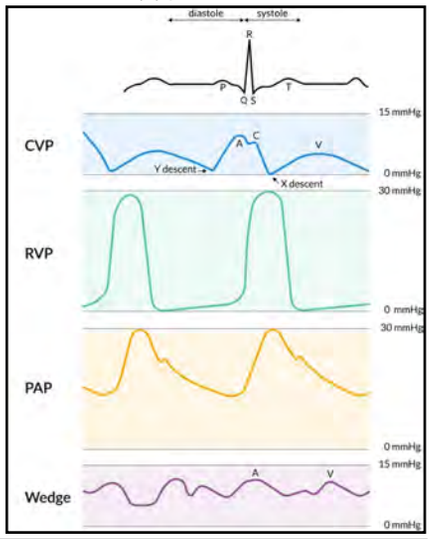


Elaine Fletcher

Cardiology — Pulmonary Artery Catheterization

Overview

- Indications: PA catheter (PAC) for tailored therapy; diagnose (1) etiology of shock (e.g. cardiogenic vs. distributive); (2) cardiogenic vs. non-cardiogenic pulm edema; (3) LV vs RV failure; (4) etiology of PH; (5) L→ R shunting; (6) valve disease; (7) pericardial disease
- Efficacy: controversial - ESCAPE trial (JAMA 2005;294:1625) showed no mortality benefit to empiric use of PAC in pts w/ ADHF not on inotropes. PACs are still standard of care and guideline-recommended in carefully selected patients (e.g. cardiogenic/mixed shock on inotropes/pressors or in pts w/ MCS)(Circulation 2022;145:e895–e1032)
- Line course: central vein (IJ/fem)→SVC/IVC→RA→RV→PA→distal pulmonary arteriole

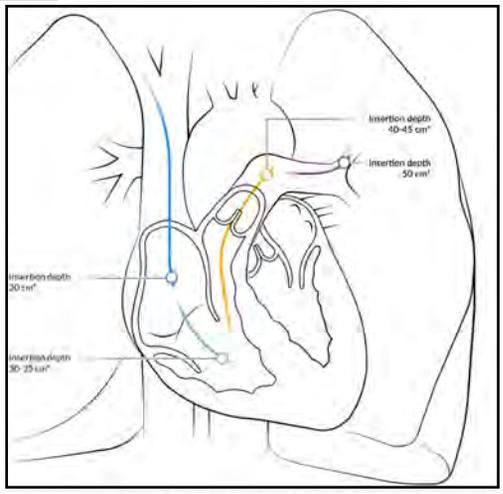


Venous Waveforms (CVP/PCWP)

- **a wave**: atrial contraction; coincides with the QRS complex (on CVP tracing)
- **c wave**: bowing of TV into atrium during ventricular contraction; more visible in 1st degree AV block.
- **x descent**: atrial relaxation (early x descent), downward movement of TV (late x descent)
- **v wave**: passive atrial filling (venous return) when TV/MV closed; coincides with T wave
  - Prominent v waves seen in MR & TR
- **y descent**: rapid atrial emptying following opening of the TV (ventricular diastole)
  - Prominent x+y descents seen in pericardial constriction; blunted y descent seen in tamponade

Obtaining PA Line Numbers on AM Rounds

1) Position patient supine with head-of-bed between 0-60°
2) Align transducer with mid-axillary line (4th intercostal space)
3) Zero transducer to air & assess waveform for dampness
4) Record PA systolic, PA diastolic, PA mean, CVP, & line position
5) Open the PA catheter balloon port & remove 1.5cc air
6) Inject 1.5cc air slowly until PCWP waveform observed (use minimum air required to ↓ risk of PA infarction/rupture) & record PCWP (limit balloon inflation <10 seconds)
7) Release safety syringe & allow balloon to deflate passively; verify balloon deflated by visualizing the PA waveform
8) **Troubleshooting**: CXR to evaluate position
   a. **Arrhythmia**: catheter may be in RVOT; consider repositioning
   b. **Dampened waveform**: kinked tubing, air/thrombus, or catheter tip against vessel wall; flush and/or withdraw catheter
   c. **No PCWP tracing**: catheter tip is not far enough, balloon has ruptured, or catheter is coiled in RV
   d. **Continuous PCWP**: catheter tip is advanced too far
   e. **mvO2 resembles arterial O2**: catheter tip is advanced too far



Calculating Hemodynamic Parameters

- Normal: "rule of 5s" → RA 5, RV 25/5, PA 25/10, PCWP 10, LV 125/10
- Cardiac output: TD better predicts mortality (JAMA Cardiol 2017:10:10)
  - **Fick** = VO_2 / (13.4 * Hgb * [SpO_2 – MvO_2]) [*nml*: 4-7 L/min]
    - VO_2 ≈ 250 ml/min *OR* 3*wt(kg) *OR* 125*BSA
  - **Thermodilution** (**TD**): temp change (measured by thermistor in PA) is proportional to LV CO (inaccurate if: TR, intracardiac shunt, very low CO)
- Cardiac index = CO/BSA [*normal*: 2.6-4.2 L/min/m^2]
- SVR = (MAP-CVP) / CO x 80 [*normal*: 700-1200 dynes*s*cm^5]
- PVR = (mPAP-PCWP) / CO [*normal*: <2 Woods units]

Hemodynamic Profiles of Shock

Subtype	CVP [JVP]	PCWP [CXR]	CO/CI [MvO2, UOP]	SVR [cap. refill]
Hypovolemic	↓	↓ [nl]	↑ [var, ↓]	↑ [delayed]
Cardiogenic	↑	↑ [nl, wet]	↓ [↓, ↓]	↑ [delayed]
Septic	Var	Var [nl, wet]	↑ [↑, ↓]	↓ [normal]
RHF or PE	↑	N [nl, large PA]	Var [var, nl to ↓]	Var [nl to ↓]
Tamponade	↑	↑ [nl, large heart]	↓ [↓, ↓]	↑ [delayed]

Hemodynamic Considerations

- All quantitative pressure measurements (*especially PCWP*) should be made at **end-expiration** (when intrathoracic pressure is zero)
  - Spontaneous respiration: **RA & PCWP ↑ with expiration** → measure from the *higher* a waves ("patient = peak")
  - Positive pressure ventilation: **RA & PCWP ↓ with expiration** → measure from the *lower* a waves ("vent = valley")
- Measure RA & PCWP at **end-diastole** (i.e. just before the **c wave**)
- Correlate PCWP with PA diastolic pressure; if well correlated, can trend PAd as proxy for PCWP (allowing for less frequent wedging)

Clinical Considerations

- Placement: usually through RIJ Cordis. Advance ONLY with balloon inflated. Deflate balloon when withdrawing and at ALL other times. Must have cardiology or pulmonary fellow present to place/advance at MGH.
  - Cath lab if: severe PH (>70mmHg), large RV/RA, LBBB, PPM/ICD <6mo, temp wire, severe TR, prosthetic TV/PV, femoral access
- Contraindications: absolute – insertion site infection, RVAD, RA/RV mass/thrombosis, mechanical TV/PV, endocarditis (TV/PV)
- Position: on CXR, should be in middle 1/3 of the chest bilaterally; ability to wedge more important than CXR position
- Complications: infection, bleeding, PTX, VT, RBBB, CHB, PA rupture (place patient on side with the catheter "bleeding side down", order STAT CXR, CBC, coags, CT surgery consult), pulm infarct, PE, catheter knotting (difficult removal)

Tom Sommers

Cardiology

Cardiac Devices: PPM, ICD, & CRT

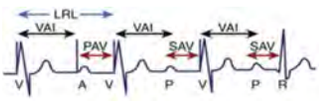
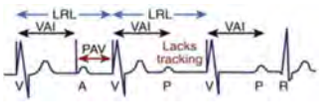
Permanent Pacemakers (PPM), Implantable Cardioverter-Defibrillators (ICD), & Cardiac Resynchronization Therapy (CRT)

- Types: single chamber (RA or RV lead), dual chamber (RA + RV leads), biventricular (RV + coronary sinus ± RA leads)
- PPM: sense/pace the RA & RV to treat bradyarrhythmias (see tables for nomenclature and common modes)
- ICD: device with an RV lead capable of terminating re-entrant ventricular tachyarrhythmias via pacing, cardioversion, or defibrillation
- CRT: provides simultaneous RV + LV pacing in HFrEF pts w/ wide QRS to ↓dyssynchrony → LV reverse remodeling & ↑LVEF
  - CRT-P = BiV ± RA pacing; CRT-D = CRT-P w/ ICD function

Hardware Overview

- System consists of pulse generator + leads. Usually implanted SQ in upper chest (L>R) >> abdominal
- Types: **traditional** (SQ pulse generator + intracardiac leads), **leadless** (Micra, pulse generator directly implanted into RV; no pocket complications; when battery dies, device retrieval is rare), **SQ ICD** (no IV hardware; low risk for infection but NO pacing capabilities)
- Placement: RA lead → RA appendage; RV lead → RV apex; LV lead → coronary sinus → branches of great cardiac vein
- Interrogation: EP Technician (p16939) business hours; EP fellow on call after-hours/weekend
- MRI compatibility: not all devices are MRI compatible (find out device model), however, even non-MRI compatible devices may be safe to scan after re-programming (NEJM 2017;376:755). Case-by-case.
- Magnet response: PPM: asynchronous pacing (DOO/VOO); ICD: suspends detection/treatment of tachyarrhythmias (no effect on pacing)

NASPE/BPEG Codes for Pacing Operating Modes			
Position I	Position II	Position III	Position IV
Chamber(s) Paced	Chamber(s) Sensed	Response to Sensing	Rate Modulation
O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	T =Triggered	R = Rate Modulation
V = Ventricle	V = Ventricle	I = Inhibited	
D = Dual (A+V)	D = Dual (A+V)	D = Dual (T+I)	

Code	Action	Use	Waveform
Single Chamber Modes			
AAI	Atrial Demand; A-paced, A-sensed, atrial activity inhibits PM	Isolated SN dysfxn, intact AV node	
VVI	Ventricular Demand; V-paced, V-sensed, ventricular activity inhibits PM	High-grade AVB, bradycardia; does not track atrial activity (i.e. chronic AF)	
AOO/ VOO	Asynchronous; A- or V-paced, no sensing	AOO: Obsolete, VOO: Temp wire pacing	
Dual Chamber Modes			
Tracking Modes			
DDD	Synchronous; paces senses in A & V; atrial activity is tracked/triggers ventricular activity	Allows coordination of A- & V-pacing; most closely mimics intrinsic conduction system	
VDD	Atrial Synchrony Possible; V-paced, A- & V-sensed	Rarely used; high-grade AVB	
Non-Tracking Modes			
DDI	AV Sequential; paces & senses in A & V; atrial activity not tracked; atrial tachyarrhythmia does not trigger RVR	SSS or sinus brady with intermittent atrial tachycardias	
DOO	Asynchronous Fixed Rate; paces A & V, no sensing	Avoid sensing electrocautery or electromagnetic interference	

Different pacing modes. LRL, *Lower rate limit;* P, *intrinsic P wave;* A, *atrial paced event;* R, *intrinsic R wave;* V, *ventricular paced event;* VAI, *ventriculoatrial interval;* PAV, *paced atrioventricular interval;* SAV, *sensed atrioventricular interval.*

PPM Indications (Class I) (JACC 2019;74:e51)

Sinus Node Dysfunction:

- Symptomatic sinus brady (± sinus pauses) or chronotropic incompetence (after tx reversible causes, ensure symptoms temporally correlated)
  - Recommend DDD for symptomatic SND with extension of AV interval to minimize V-pacing; prefer physiologic pacing
- Symptomatic medication-induced bradycardia if there is no accepted alternative medication
- Permanent AF and symptomatic bradycardia

AV Block (AVB)/Conduction Disease:

- 3°AVB with or without symptoms
- Symptomatic 2° AVB Mobitz I or II (conduction disease must correlate temporally w/ symptoms)
- Permanent 2° AVB Mobitz II or intermittent 3° AVB (regardless of symptoms)
- Alternating bundle branch block

Neurocardiogenic: only if syncope associated with marked cardioinhibitory or bradycardic event

ICD Indications (Class I) (JACC 2018;72:e91, 2022 AHA HF Guideline)

- 1° prevention indicated for pts with HFrEF only if after re-assessment on optimal GDMT for ≥90d. All pts must have an estimated >1-year survival.

Primary Prevention	Secondary Prevention
Ischemic CM: NYHA Class I: EF ≤30%, >40d s/p MI & ≥90d s/p revascularization NYHA Class II/III: EF ≤35%, >40d s/p MI & ≥90d s/p revascularization Other: EF ≤40%, >40d s/p MI + NSVT + inducible VT/VF	- Prior episode of cardiac arrest (VF/pulseless VT) and unstable or sustained stable VT** in presence of other heart disease/channelopathy or if no reversible cause found - Cardiac syncope w/ LVEF<35% OR cardiac syncope w/ inducible VT/VF on EP study OR cardiac syncope where VT/VF is most likely etiology **Does not include patients who have VT/VF limited to within 48h of MI
Non-ischemic CM*: EF ≤35% + NYHA Class II/III	
- HoCM with known arrhythmias or after risk stratification (Circ 2024;149) - Long QT syndrome refractory to ßB +/- cardiac denervation - Arrhythmogenic right ventricular cardiomyopathy after risk modeling - Cardiac sarcoid (LVEF ≤35% despite GDMT and immunosuppression) (Circ 2024;149) Also considered in: Brugada syndrome, catecholaminergic pVT, channelopathies, and specific protein variants (LMNA/C, desmosomal proteins, phospholamban, Filamin-C)	

*DANISH (NEJM 2016;375:1221) in pts w/ NICM, ICD ↓SCD, but no Δmortality; In SCD-HeFT (JACC 2020;76(4):405) no benefit from ICD in NICM subgroup

CRT Indications (Class I) (2022 AHA HF Guideline)

- NYHA II-III or ambulatory IV + LVEF ≤35% + Normal Sinus Rhythm + QRS >150ms w/ LBBB

Elaine Fletcher

AORTIC STENOSIS

- **Etiology**: Aortic sclerosis (calcification of the valve; increasingly common with age), bicuspid valve (most common cause <70yo), rheumatic heart disease (leaflets fuse, often with concurrent MV disease), radiation-induced
- **Clinical Manifestations**: most important determinant of prognosis = sxs: 50% mortality at 5y if angina, 3y if syncope, 2y if HF
  - Angina: ↑afterload → ↑LV pressures → LVH → ↑O2 demand → supply-demand mismatch w/ exertion or tachycardia
  - Syncope: exercise-induced vasodilation → inability to augment CO due to stenotic valve→ hypotension / transient hypoperfusion
  - Heart failure (dyspnea): LVH → diastolic dysfunction (*systolic dysfunction is a late finding*)
  - Acquired vWF def: 20% of severe AS, can worsen bleeding from GI AVMs "Heyde syndrome" (NEJM 2012;367:1954)
- **Diagnosis**:
  - Physical exam: harsh crescendo-decrescendo murmur at RUSB radiating to carotids. **If severe**: murmur late-peaking, delayed carotid upstroke (pulsus parvus et tardus), soft S2 (Am Heart J 1999;137:298); Pearl: soft murmur may indicate low flow!
  - TTE: measure mean (not peak) gradient, valve area, & jet velocity; also, important to assess EF (gradient can be underestimated with **reduced EF → low flow, low gradient AS**)
- **Severe AS**: peak AV velocity ≥4m/s, **mean** AV pressure grad **≥40mmHg**, or AV **area (AVA) ≤1cm²** (ACC/AHA: Circ 2021;143:e35)
  - ECG: LVH, LAE, LAFB, LBBB
  - Exercise stress testing: recommended in asymptomatic severe AS to assess for symptoms; do **not** perform in pts w/ sx
- **Natural History**: highly variable, but on average, AVA ↓ ~0.1 cm²/y & mean gradient ↑8mmHg/y (JACC 1989;13:545). Patients with bicuspid valves, advanced age, & those with severe leaflet calcification are at risk for more rapid progression
- **Aortic Valve Replacement (AVR)** (J Am Soc Echo 2018;31:117): determining indication for valve replacement is based on evaluating: (1) presence of **symptoms,** (2) **severity** by TTE criteria, (3) LV function (**EF**)
  - Symptomatic, severe AS (Stage D): prompt AVR indicated due to risk of sudden death
  - Asymptomatic, severe AS (Stage C): AVR appropriate if LVEF<50%, if symptoms provoked with exercise testing, or undergoing other cardiac surgery; for patients with asymptomatic very severe AS (AVA ≤0.75cm²) early surgery may have mortality benefit (NEJM 2020;382:111)
  - If suspect **low-flow** (LVEF <50%) & **low-gradient** (<40mmHg w/ AVA <1cm²): **dobutamine stress TTE (DSE)** to distinguish between low-flow, low-gradient AS versus "pseudosevere AS" (Circ 2011;124:739)
    - Low-flow/Low-gradient: if DSE = V_{max} >4m/s or mean gradient >40mmHg while AVA remains <1cm², AVR *is* indicated
    - Pseudosevere AS: if DSE results in AVA >1cm², AVR not indicated
  - **Bioprosthetic vs Mechanical:** if contraindications to AC with VKA, must offer bioprosthetic; if pt <50 years of age without contraindications to AC, SAVR w/ mechanical valve recommended (COR 1; Circulation 2021; 143:35); if >65 yrs of age, bioprosthetic recommended (COR 2a); 50-65 years of age require shared decision making
  - **SAVR vs TAVI for bioprosthetic**: pts <65y, SAVR recommended d/t increased durability; >80y TAVI recommended
    - 65-80 yrs of age: depends on surgical risk (STS-PROM score), concomitant heart/vascular disease, valvular/vascular anatomy that is amenable to TAVI (Circulation 2021; 143:35)
    - TAVI is recommended for those at extreme surgical risk (compared to medical therapy, PARTNER); noninferior to SAVR in those at high (NEJM 2011;364:2187), intermediate (PARTNER 2), & low surgical risk (PARTNER 3). Valve-in-valve TAVI may additionally be beneficial in pts with surgical bioprosthetic AV failure (JACC 2017;69:2253)
  - **TAVI Evaluation**: c/s **structural cardiology**, **cardiac surgery**. Obtain **TTE**, TAVI-protocol **CT**, **dental clearance** (Panorex)
  - **TAVI Complications**: Valve: embolization, paravalvular leak; Stroke: embolic (first 48h), ischemic/hemorrhagic; Conduction: HGAVB requiring PPM (Major RF: baseline RBBB, need for pacing or HAVB s/p TAVI; Minor: h/o AF, valve oversized >15%; Card Fail Rev 2021; 7:e12); Bleeding; Access site complication; Hemodynamics: dynamic LVOT obstruction due to LVH ("suicide LV"), HTN (sudden ↓ in obstruction after TAVI), hypotension (d/t ↓preload), tamponade (perforation, usually immediate); AKI
- **Medical Management**: *AS is a surgical disease & medical management is only utilized for treatment of sx*
  - Treat HTN: reduce the "double load" on the ventricle. In theory, ACE-I may have beneficial effect on LV fibrosis. However, no optimal regimen exists because anti-hypertensives can lead to hemodynamic issues. Bottom line: **start low and go slow**
  - Control volume status: operate within a narrow preload range, prone to underfilling (low preload) & overfilling (volume overload)
- **Anticoagulation after Valve Replacement**:
  - Bridging UFH or LMWH if AC interrupted only in mechanical MV or mechanical AV with RFs (Class I),
  - RFs: AF, LV dysfxn, prior VTE, hypercoag, older gen mech AVR (Circ 2021;143:e35)
  - Bleeding risk: mechanical > bioprosthetic (likely AC related). Reoperation risk: bioprosthetic > mechanical
  - TAVI: ASA monotherapy non-inferior to DAPT for thrombotic events & associated with less bleeding (NEJM 2020;383:1447)
  - If need AC for AF, DOACs similar outcome after TAVI, not approved for valvular MS (moderate+) (JAHA 2021;11:e023561)

Prosthesis	Location	Timing and Risk Factors for AC	INR	Class
Mechanical	**Mitral**	Indefinitely	**2.5-3.5 (+ ASA 81)**	I
	Aortic	Indefinitely, (+) risk factors	**2.5-3.5 (+ ASA 81)**	I
		Indefinitely, (-) risk factors	**2.0-3.0 (+ ASA 81)**	I
Bioprosthetic	**Mitral**	First 3 months after placement, regardless of RFs	**2.0-3.0 (+ ASA 81)**	IIa
		>3 months after placement	**ASA 81**	IIa
	Aortic	First 3 months after placement, regardless of RFs	**2.0-3.0 (+ ASA 81)**	IIa
		>3 months after placement	**ASA 81**	IIa
TAVI	**Aortic**	No AC; indefinite antiplatelet monotherapy	**ASA 81 or Clopidogrel 75**	IIa

Cardiology

Valvular Heart Disease

Aortic Regurgitation (aka Insufficiency)

- **Etiology**: Acute: aortic dissection, valve perforation (usually due to MI or endocarditis), traumatic valve leaflet rupture; Chronic: leaflet abnormalities (bicuspid valve, endocarditis, RHD) or root dilation (secondary to HTN, CTD, dissection, syphilis)
- **Pathophysiology**: Acute: diastolic regurgitant flow → *sudden* ↑LVEDP (w/o remodeling time) → ↓CO → pulmonary edema; Chronic: diastolic regurgitant flow → ↑LVEDP → initial maintenance of SV/CO → progressive ventricular dilatation → failure
- **Clinical/Exam**: angina, L-sided HF. Acute: cardiogenic shock. Chronic: ↑pulse pressure (bounding pulses, bouncing head/uvula, nail bed capillary pulse; Int J Card 2006;107:421)
  - Auscultation: high-pitched, blowing diastolic decrescendo murmur along LSB. Longer murmur = more severe/chronic. May hear low-pitched diastolic murmur at apex secondary to regurgitant jet displacing anterior mitral leaflet
- **Treatment:**
  - Acute: usually needs surgery. Nitroprusside to ↓afterload; ino- and chronotrocpes to ↓diastolic time. **Do not use vasoconstrictors or IABP** (which worsen regurg) **or beta-blockers** (which block compensation and ↑diastolic regurgitant time)
  - Chronic: ACEi/ARB/Entresto first line, CCB or hydralazine/nitrates second line to reduce LV afterload. Proceed to AVR if: symptomatic severe AR; LVEF<55%, LV end-systolic dimension >50mm, undergoing other cardiac surgery

Mitral Stenosis

- **Etiology**: 80% due to RHD (only 50-70% report h/o rheumatic fever). Also, endocarditis, annular calcification (rarely significant), congenital, autoimmune valvulitis (SLE), carcinoid synd, endomyocardial fibroelastosis, XRT (e.g., 10-20y after Hodgkin's tx)
- **Pathophysiology**: elevated LAP → pHTN, **AFib (47%)**. Demand for ↑CO precipitates symptoms. Valve narrows ~0.1cm^2/y
- **Clinical/Exam**: dyspnea (most common), pulmonary edema, hemoptysis, VTE even w/o AFib (Am Heart J 2000; 140:658), RV failure
  - Auscultation: loud S1, high-pitched opening snap (more severe if earlier, indicating higher LAP); low-pitched diastolic rumble at apex and at end-expiration
- **Treatment:** Medical: warfarin if LA thrombus, AFib, prior embolism (Class I) or LA > 55mm (Class IIb). Beta-blockers if tachycardic or dyspneic, diuresis if pulmonary vasc congestion. If rheumatic, secondary ppx against strep as below (Circulation 2021;143:e35)
  - Intervention: generally, need to have severe MS (MV area ≤1cm^2) + symptoms to be considered for intervention
    - **Rheumatic MS:** symptomatic pts with severe rheumatic MS and favorable valve morphology (based on TTE, Wilkins Score) → **Percutaneous mitral balloon commissurotomy (PMBC)** (COR 1, Circulation 2021;143:e35); consider if asymptomatic and elevated pulmonary pressures (>50mmHg; COR 2a) or new AF (COR 2b)
    - **Nonrheumatic Calcific MS:** because calcification involves the annulus and base of the leaflets without commissural fusion, there is no role for PMBC or surgical commissurotomy; consider intervention only after discussion of high risk (COR 2b)
    - Proceed to MVR if not PBMC candidate, PBMC fails, or undergoing another cardiac surgery (even if asymptomatic)

Mitral Regurgitation

- **Etiology**: dilated annulus ("functional MR"), MVP, ischemic papillary muscle dysfunction, ruptured chordae, endocarditis, RHD, CTD
- **Pathophysiology**: LA/LV volume overload → LV dysfxn, progressive enlargement of LV → dilated mitral annulus → regurgitation
- **Clinical**: Acute: flash pulmonary edema, hypotension, shock; Chronic: DOE, orthopnea, PND, AFib, pulmonary → periph edema (pulmonary edema may be one-sided depending on jet direction)
- **Exam**: holosystolic murmur at apex radiating to axilla, S3, displaced PMI. If acute: early diastolic rumble and S3 may be only signs
- **Treatment:**
  - Acute: ↓afterload (e.g., nitroprusside), inotropes (dobutamine), diuresis. If hemodynamically unstable (esp. post-MI or endocarditis), consider IABP and/or urgent surgical repair (NEJM 2012;366:2466). If ischemic, consider revascularization
  - Chronic: GDMT for HF if applicable
    - **Severe primary MR**: symptomatic w/ any EF *OR* asymptomatic w/ EF ≤ 60% or LVESD ≥ 40mm → MVR (Circulation 2021;143:e35); primary MR w/ high surgical risk, transcatheter edge to edge repair (M-TEER) (COR 2a; EVEREST II).
    - **Severe "functional MR":** if LVEF ≥50% OR unfavorable anatomy AND symptomatic on maximal GDMT OR undergoing CABG → MVR; if LVEF <50% AND persistent symptoms on maximal GDMT AND anatomy favorable → M-TEER (COAPT).

Tricuspid Regurgitation

- **Etiology**: Primary: RHD, IE, iatrogenic (device leads, etc), congenital, trauma, carcinoid, drugs; Secondary: pulmonary HTN w/ RV remodeling ("functional"), dilated annulus (associated with AF), dilated CM, RV volume overloadischemic papillary muscle dysfunction
- **Pathophysiology**: similar to mitral regurgitation, but involving RA/RV and tricuspid annulus
- **Clinical**: Right-sided heart failure: hepatosplenomegaly, ascites, peripheral edema, large V in JVP, pulsatile liver, substernal pulsation
  - Ausculation**:** holosystolic murmur at left mid- or lower- sternal border that increases with inspiration, S3
- **Treatment: Medical:** Diuresis (COR 2a), management of underlying cause
  - **Tricuspid valve replacement:** Consider if primary severe TR OR secondary severe TR with RV dilation/dysfx
    - Primary severe TR: if: 1) at time of LV valve surgery, 2) R heart failure, 3) moderate TR with progressive RV dilation/dysfx
    - Secondary severe TR if: 1) R heart failure poorly responsive to GDMT without ↑PAP or left HF (Circ 2021;143:e35).
    - Progressive TR (Stage B): consider if undergoing L valve surgery OR tricuspid annular dilation >4 cm w/ R heart failure
    - Transcatheter therapies are potential options but lack longterm outcomes and performance data (JACC 2018;71:2935)

General Principles

- **Rheumatic Disease:** secondary ppx against streptococcus recommended for 10y or until 40 yrs old (whichever longer, COR I)
- **AF and Valvular disease:** w/o mechanical valve, DOAC reasonable VKA except in rheumatic MS, practice variable for nonrheum MS
- **IE Prophylaxis:** Reasonable in pts undergoing dental manipulation with 1) prosthetic heart valves, 2) prosthetic material used in valve repair, 3) prior IE, 4) Unrepaired cyanotic CHD, or 5) s/p cardiac transplant with valve abnormality (COR 2a; Circulation 2021; 143:35)

Cardiology

Pericardial Disease

CARDIAC TAMPONADE

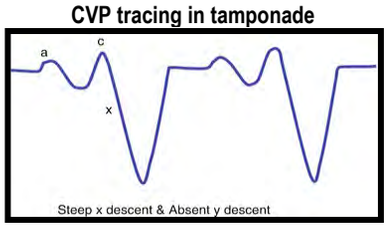
- Definition: hemodynamic insufficiency caused by impaired cardiac filling due to ↑pericardial pressure due to effusion, leading to ↑intracardiac chamber pressures & eventually equalization of diastolic pressure in all 4 heart chambers
- Etiologies of pericardial effusion: idiopathic (20%), iatrogenic (16%), malignant (13%), uremic, infectious, HF, autoimmune (Am J Med 2000;109:95). Tamponade more likely in malignant, post-viral (including SARS-CoV-2), uremic, iatrogenic (i.e. post-cath) etiologies. Also seen with prox. aortic dissection & myocardial wall rupture

Clinical Manifestation and Diagnosis:

- Beck's Triad: ↓BP, ↑JVP, muffled heart sounds; *elevated BP does not rule out*
- Pulsus paradoxus (PP): exaggeration of normal decrease in SBP during inspiration (If >10mmHg, ⊕LR=3.3. If ≤10 mmHg, ⊕LR=0.03)
    1. Slowly deflate BP cuff→note pressure when systolic Korotkoff sounds only heard during expiration (will sound irregular) (**a**) → continue slowly deflating BP cuff until Korotkoff sounds heard throughout; (**b**) **PP = a – b**
    2. Via A-line tracing (**PP = height exp. – height insp. systolic waveform**)
    - False-negative PP conditions: pre-existing disease w/ ↑LVEDP (e.g., chronic HTN), regional tamponade, pericardial adhesion, acute MI, arrhythmia, ASD/VSD, severe AI, hypotension/shock, RVH)
    - PP DDx: severe COPD/asthma, massive PE, hypovolemic shock, RVMI, constrictive physiology, tense ascites
- ECG: sinus tach, low QRS voltage (50%; limb ≤5mm, precordial ≤10mm), electrical alternans (20%; precordial leads)
- TTE: inspiratory leftward septal shift, diastolic collapse of cardiac chambers (R > L-sided), respirophasic changes in transvalvular velocities, IVC plethora. SIZE of effusion does NOT predict tamponade – **RATE of accumulation is more important**

5 Clinical Features Associated with Tamponade (JAMA 2007;297:1810)		
Sign/Sx	**Sensitivity**	**95% CI**
Dyspnea	87-89%	n/a
Tachycardia	77%	69-85%
Pulsus paradoxus	82%	72-92%
Elevated JVP	76%	62-90%
Cardiomegaly on CXR	89%	73-100%

CVP tracing in tamponade



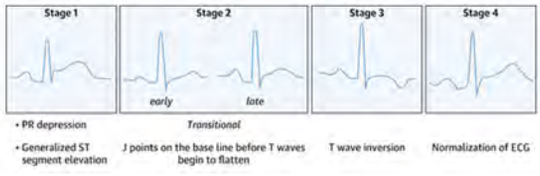
Treatment:

- **Fluid resuscitation**: administer volume urgently to increase intracardiac pressures (monitor closely as overfilling can worsen tamponade), starting w/ 250-500cc bolus; greatest benefit for SBP < 100 mmHg (Circ 2008;117:1545)
- Inotropes: administer if IVF insufficient. Unclear benefit b/c endogenous catecholamines already at max level. **Avoid BB**
- PPV: avoid if possible as ↑positive intrathoracic pressure will further impede ventricular filling
- Drainage: catheter **pericardiocentesis**, surgical pericardiectomy (if aortic/myocardial rupture), or HD (if uremic)
    - Analysis of pericardial fluid: cell count, total protein, LDH, gram stain/cx, viral markers/cx (Coxsackie, HSV, CMV, EBV, HIV), AFB smear/cx, ADA/IFN-gamma/lysozyme (if concerned for TB), cytology/tumor markers
    - Removal of drain: when output **<50cc/d**, otherwise consider **pericardial window** (pleural>abdominal). See *Pericardial Drain*

PERICARDITIS

- Classification: acute (<6w), incessant (>6w w/o remission), recurrent (return after symptom free interval of 4-6 wks), chronic (>3months)
- Epidemiology: 5% of pts in ED w/ non-ischemic chest pain, M > F
- Etiology: 80-90% idiopathic (usually viral/post-viral), bacterial, fungal, post-MI, uremic, mycobacterial (TB), autoimmune (CTD, vasculitis), malignancy (e.g. lung, breast), XRT, drugs (procainamide, hydral, INH) (NEJM 2014;371:2410)

ECG Evolution in Pericarditis (JACC 2020;75:76)



Clinical Manifestations and Diagnosis:

- Symptoms: sudden onset, pleuritic, retrosternal **CP relieved w/ sitting up & leaning forward** (may radiate to trapezius muscles), ± viral prodrome if infectious etiology. In uremic or CTD pericarditis, CP may be absent
- Exam: pericardial **friction rub** (~30% cases), best heard at LLSB w/ diaphragm of stethoscope at end-expiration w/ pt leaning forward
- ECG: 4 stages: (1) **diffuse ↑ST & ↓PR** (↑PR & ↓ST in aVR/V1); (2) ST & PR normalize; (3) diffuse TWI; (4) TW normalize. May see continual low-voltage or electrical alternans if effusion present. Uremic pericarditis: ECG can be normal b/c epicardium not inflamed
- Diagnosis: ≥2 of the following: (1) characteristic CP, (2) friction rub, (3) suggestive ECG changes**,** (4) pericardial **effusion**
    - Workup: infectious w/u, BUN/Cr, ANA/RF/CCP, HIV, HCV, IGRA, ESR/CRP, troponin (elevated in ~30%, c/f myopericarditis)
    - TTE: assess for presence/size/location of co-existent effusion and/or tamponade physiology
    - Pericardiocentesis/Surgical Drainage: if (1) suspect **malignancy** or **bacterial** etiology (2) large effusion (>2cm) (3) tamponade
    - Cardiac MRI: adjuvant test if dx uncertain or c/f myocardial involvement; +LGE has 94% Sn for pericarditis (JACC 2020;75:76)

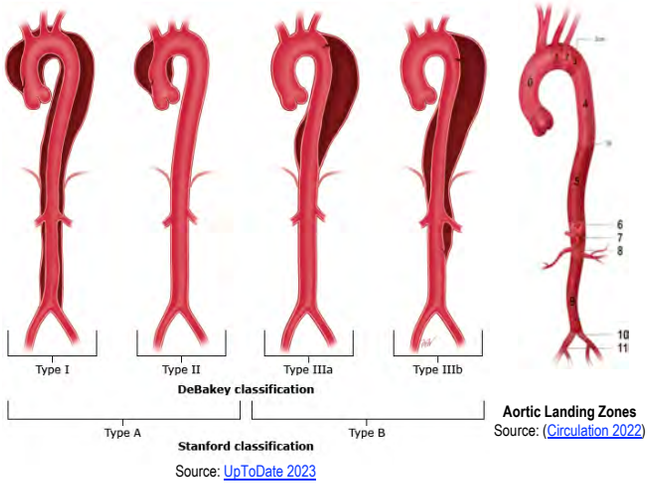
Treatment: self-limited (days-weeks) in 70-90% of cases

- Hospitalize if: fever, ↑WBC, large effusion (>2cm), immunocompromised, anticoagulated, trauma, ↑troponin, unstable/signs of tamponade, failure to respond to NSAIDs after 7d. Also consider hospitalization if subacute presentation
- 1st-line treatment: **NSAIDs** (e.g. ibuprofen 600-800mg TID; ASA 650-1000mg TID) ± **colchicine** 0.6mg BID (qd if pt <70kg)
    - **Colchicine** ↓sx at 72h, improves 1w remission and 18mo recurrence in acute idiopathic pericarditis (Circ 2005;112:2012; NEJM 2013;369:1522). No benefit w/ malignant or uremic cases
    - **ASA**: preferred over NSAIDs if: post-MI, CAD, concomitant anti-platelet/anticoagulant therapy
    - Activity restriction: avoid strenous activity until symptom resolution
- **Glucocorticoids** (prednisone 0.2-0.5mg/kg/d): preferred over NSAIDs if: sx refractory to 7d of NSAID treatment, recurrent (>2 episodes), uremic pericarditis, CTD pericarditis, or contraindication to NSAIDs. Associated w/ ↑recurrence if first idiopathic episode
- Duration: *NSAIDs*: until sx resolve (1-2w), then taper (total 3-4w). *Colchicine*: 3mo. *Glucocorticoids*: 2w, then taper (3mo total)

ACUTE AORTIC SYNDROMES (AAS) (Nat Rev Cardiol 2015;12:103)(Lancet 2023;401:p773)

Definitions: three distinct processes with risk of rupture

- Aortic dissection (AD): intimal tear resulting in a false lumen
- Intramural hematoma (IMH): rupture of vasa vasorum causing hematoma within aortic wall without tear
- Penetrating aortic ulcer (PAU): ulceration of atherosclerotic plaque that penetrates into intima of aortic wall



Classification:

- DeBakey: type I (ascending + descending aorta); type II (ascending aorta only); type III (descending aorta only)
- Stanford: type A (ascending ± descending); type B (descending only)
- Aortic Landing Zones: Classification used to guide intervention

Epidemiology:

- Prevalence: aortic dissection most common (62-88%), followed by IMH (10-30%) & PAU (2-8%)
- Risk factors: male, HTN, age 60-70 (if <40yo, think Marfan syndrome, Ehlers-Danlos Syndrome type IV, CTD, bicuspid valve), atherosclerosis, prior cardiac surgery, aortic aneurysm, FHx of AAS, aortitis, trauma, pregnancy
- Aortic dissection prognosis:
  - Type A: mortality at 3y among patients discharged alive: *Medical:* 31%, *Surgical:* 10% (Circ 2006;114:I350)
  - Type B: *Medical*: 8% in-hospital mortality, 15% 1y, 24% 3y, 57% 10y (J Vasc Surg 2021;73:48)
- IMH will progress to complete dissection in 28-47% of cases. PAU will progress to aortic rupture in 42%.

Diagnosis:

- Clinical features: AD, IMH, & PAU cannot be distinguished by presentation alone
  - Signs: AI murmur, pulse deficit, upper extremity BP differential (>20mmHg), decompensated heart failure
  - Sx: chest or back pain (radiates to neck/jaw if ascending; back/abdomen if descending; may migrate as dissection propagates)
- Complications: syncope, shock, branch artery occlusion (MI, CVA, paraplegia, cold extremity, renal failure); aortic valve regurgitation, pericardial effusion, cardiac tamponade, stroke
- Risk Score: Aortic Dissection Detection Risk Score (ADD-RS): d-dimer versus directly to CTA (Circ 2018;3;250)
- Labs: *rule out* if **D-dimer** <500ng/mL (96% NPV), **troponin** (can be ⊕ if dissection extends into coronaries), ↑**MMP-9**
- Imaging:

CXR	- 50% with AAS have normal CXR; only 1/3 will have widened mediastinum
CT-A	- Sn 95%, Sp 87-100%; **first-line modality** in pts w/ high clinical probability of AAS - Combined I+/I- (assess for IMH, mediastinum hemorrhage, or hemopericardium)
TTE	- Sn 73-100%, Sp 71-91%, least accurate of diagnostic imaging modalities - Useful for identifying AV dysfunction, prox dissections extending to Ao root/pericardium
TEE	- Sn 99%, Sp 90-100%. Often used intra-op to confirm dx prior to surgery - Invasive nature limits use; cannot detect pathology below the diaphragm

Management:

- Goal: "**impulse control**" → minimize aortic wall stress by ↓LV ejection force (**dP/dT**): goal HR <60, SBP 100-120mmHg
- Agents:
  - **IV beta blockade** (esmolol, labetalol); **except** if acute severe AI.
  - If additional BP control required, consider IV nitroprusside, TNG, nicardipine. If refractory HTN, consider renal artery involvement.
    - **NEVER** use vasodilators for AA without AI without concomitant beta blockade → will increase wall stress via reflex tachycardia, thereby increasing dP/dT. **Opiate analgesia** attenuates release of catecholamines (Lancet 2015;385:800)
- Urgent surgical consultation (CT surgery)
- Aortic Dissection:
  - **Type A**: immediate open surgical repair 26% mortality vs >50% with medical management (JAMA 2000;283:897)
  - **Type B**: *uncomplicated*: medical therapy (80% survival at 5y); *complicated* (compromise of renal/mesenteric vessels): TEVAR. However, INSTEAD-XL showed improved outcomes with low-risk preemptive TEVAR in all Type B dissections
- IMH & PAU:
  - **Type A**: urgent (i.e., within days) open surgical repair
  - **Type B**: medical management or TEVAR

AORTIC ANEURYSMS (Circulation 2022 ;146 ; e334)

	Abdominal Aortic Aneurysm (AAA)	Thoracic Aortic Aneurysm (TAA)
Epidemiology	• M>F; >65yo, mostly infrarenal	• M>F, mostly 50-70yo, 50% ascending Ao, 40% descending Ao, 10% arch
Etiology	• Usually due to **atherosclerotic disease** • RFs: **smoking, male sex, age, pre-existing atherosclerosis**, obesity, HLD, HTN, FHx	• **Atherosclerotic**: majority of cases, especially descending Ao. RFs: **smoking, HLD, HTN** • **Structural/genetic**: mostly root & ascending aorta. Causes: CTD (Marfan, Ehlers-Danlos, Loeys-Dietz), Turner, bicuspid AoV, trauma • **Infectious**: 3° syphilis, mycotic aneurysm (most common org: *Staph* spp., *Salmonella* spp.) • **Inflammatory**: GCA (~10% have TAA), Takayasu, RA, psoriasis, Behcet's, Wegener's, IgG4
Screening / Surveillance	• **ACC/AHA**: one-time abdominal US in all men >60 w/ FHx of AAA & all men 65-75 who have ever smoked • **Surveillance** (J Vasc Surg 2018;67:2): interval depends on size • 3.0-3.9cm: q2-3y; 4.0-4.9cm: q12 months; 5.0-5.4cm: q6 months	• **General population**: not recommended • **Indications**: at time of dx of Marfan, Turner, Loeys-Dietz, Takayasu or GCA. 1° relatives of pt w/ TAA, dissection, bicuspid valve (even if no disease-causing variant identified on genetic testing) • **Surveillance**: interval depends on presence of aneurysm etiology/location; primarily CT/MRI, TTE (if valvular disease) ranging from q6-12months • **Associated aneurysm:** screen for abdominal, intracranial and lower extremity aneurysms
Imaging Modalities	• **Abdominal US**: screening and surveillance of infrarenal AAAs. High Sn/Sp (>90%), operator-dependent • **CTA**: high Sn/Sp, >>US for suprarenal AAA; ECG-gated CT (synced w/ diastole via ECG) increases resolution • **MRI/MRA**: good Sn/Sp, preferred for aortic root imaging & for imaging tortuous aortas • **CXR**: "enlarged aorta" nonspecific (tortuous aorta vs aneurysm) • **TTE**: useful for root & proximal thoracic aorta; **TEE**: will visualize entire thoracic aorta but rarely used	

Treatment	**Medical**
	• **Smoking cessation** (slows growth) (J Vasc Surg 2010:52:539)
	• **Reduce BP** per ACC/AHA guidelines
	• Meds: statins (reduce all-cause mortality in pts s/p surgery)(JAHA 2018:7:19) ; BBs (have not been clearly shown to slow expansion)(J Vasc Surg 2002:35:72); ACEi (controversial); low dose ASA (may slow growth); avoid fluoroquinolones
	
	Surgical
	• Men: **>5.5cm** *OR* **growing >0.5cm/6mo or >1.0cm/y** *OR* **symptomatic**
	Women: **>4.5-5cm** (controversial)
	• Open repair vs EVAR
		Medical
		• **Reduce BP** (SBP goal of 105-120)
		• Meds: BBs (decrease TAA growth in Marfan pts), ARBs (slows expansion in Marfan pts)(JACC 2014:64:1725), ACEi, statins (goal LDL<70)
		• Behavioral: Smoking cessation, avoid straining
		• Avoid fluoroquinolones
		
		Surgical
		• Root/ascending TAAs: ± concomitant AVR
		  • Intervention indicated at 5 cm (threshold lower in patients w/ heritable conditions)*
		• Arch/descending TAAs
		  • Intervention indicated if diameter is ≥5.5 cm*
		*Repair indicated earlier if rapid expansion (>0.3-0.5cm/yr)
		
		Genetic Testing
		• Indicated in proband (first person in family in whom clinical concern is raised)
		• Genetic counseling and cascade testing if pathogenic or likely pathogenic variant detected
		• Panels include *FBN1, LOX, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, ACTA2, MYH11, MYLK, and PRKG1*

Acute Presentations	• **Rupture**: devastating mortality. Risk factors: size, rate of expansion, female gender. Sx: triad of **abd/back pain** + **pulsatile abd mass** + **HoTN** → immediate OR • **Dissection**: **pain** (chest/abdomen/back), **occlusion of aortic vessels**, **thromboembolism, discrepant blood pressure in upper extremities**	
Surgical Complications	• **Endovascular Repair:** Endoleak, graft failure, thrombosis • **Open Repair:** MI, embolization, AKI, ischemic colitis	

Cardiology

Syncope

OVERVIEW

- Definition: transient (self-limited) loss of consciousness due to cerebral hypoperfusion that is associated with loss of postural tone, followed by complete spontaneous recovery; ***excludes*** metabolic causes (e.g. hypoglycemia, hypoxia, intoxication)
- Risk assessment and need for hospitalization:
  - High-risk symptoms: preceding **palpitations**, **exertional** syncope, bleeding, syncope while supine, **lack of prodrome**, trauma
  - High-risk features: angina, CHF, mod-severe valvular or structural heart disease, ECG features of ischemia/arrhythmia, FHx of SCD, preexcitation syndromes, high-risk occupation (e.g. airline pilot), facial trauma (lack of warning time)
  - Risk calculators have high NPV (>95%) but do NOT replace clinical judgment
    - San Francisco Syncope Rule (SFSR): admit pt if ≥1: ECG changes or non-sinus rhythm, dyspnea, Hct<30, SBP<90, HF
    - Canadian Syncope Risk Score: predicts risk of 30-day serious adverse events associated w/syncope (arrhythmia, MI, etc.)
- Ddx: seizure, metabolic causes (hypoglycemia, hypoxia), intoxication/meds, vertebrobasilar TIA, fall, psychiatric, autonomic failure

ETIOLOGY AND DIAGNOSIS: (AHA/ACC/HRS: JACC 2017;70:e39)

Etiology	Historical Features	Diagnosis	Treatment
Reflex (60%) • Vasovagal • Situational • Carotid sinus syncope	Vasovagal: prodrome of dizziness, nausea, warmth, diaphoresis, pallor; a/w intense emotion, pain, stress, or prolonged standing. Situational: cough, sneeze, laugh, micturition, defecation, post exercise CSS: neck turning/ surgery/irradiation	• Vasovagal: can dx w/ tilt table test, not necessary if clear dx by history (JACC 1996;28:263) • Carotid sinus syncope: diagnose via carotid sinus massage (if no underlying bruits or CVA history)	• Avoid provocative stimuli • Isometric counterpressure maneuvers of the limbs (e.g. leg crossing, hand grip, arm tensing, Valsalva, squatting) • Meds for select cases (i.e. midodrine, fludrocortisone, βB) (NEJM 2005;352:1004)
Orthostasis (15%) • Autonomic failure (1° or 2°) • Drug-induced • Volume depletion	Prodrome of dizziness, nausea, warmth, diaphoresis, pallor Risk factors for autonomic failure: - 1°: PD, Lewy body, MSA (formerly known as Shy-Drager) - 2°: DM, amyloid, spinal cord injury, chronic EtOH, Lyme, syphilis, B12 deficiency, meds (vasodilators, diuretics, BB, TCAs, PD meds, opiates, α-blockers)	• Orthostatic vital signs (systolic ↓≥20mmHg or diastolic ↓≥10mmHg w/in 3min of standing or on a head-up tilt test ≥60°)(Circ EP 2022;15:3) - ↑HR is **NOT** part of definition - Variant: smaller, but symptomatic, reduction in SBP when supine SBP is low (90-100mmHg) but drops well below this. • Consider: Hct, A1C, SPEP if c/f amyloid, RPR, B12	• Primary: **fludrocortisone** (0.05-0.3mg qd), **midodrine** (2.5-10mg bid or tid), pyridostigmine, droxidopa (for PD-associated orthostasis) (Circ EP 2022;15:3) • Secondary: treat underlying etiology, replete volume, d/c culprit meds
Cardiac (15%) • Arrhythmia • Structural (AS, LVOT obs.) • Obstruction (e.g., PE, tamponade) • Dissection	**No prodrome**, syncope while in sitting or supine position, palpitations, FHx or personal history of heart disease	• Causes of cardiac syncope in young people (+ ECG signs): 1. WPW (delta wave) 2. HOCM (LVH, apical TWI) 3. Brugada (pseudo-RBBB with coved/saddleback pattern in V1-V2) 4. Long QTc syndrome (QTc >500ms) 5. ARVC (Epsilon wave) • **Consider cardiac monitoring** on basis of frequency and nature of syncope events (inpatient telemetry, Holter, Zio patch, implantable cardiac monitor) • **TTE only if H&P suggestive** of cardiac cause (<1% yield if no underlying heart disease and normal ECG) o ROMEO criteria: Sn 99.5%, Sp 15.4% (JHM 2018;13:823) • **Consider PE** if no other apparent cause → identified in 17.3% hospitalized w/ 1st syncope (& 25.4% w/ no other apparent cause for syncope) (NEJM 2016;375:1524)	• VT- Therapy with ablation and/or an implantable cardioverter-defibrillator (ICD) is indicated in most patients (JACC 2017:70:e39) • SVT (Less common)- If evidence of accessory pathway is found, should be treated with catheter ablation. • Bradyarrythmmias- Depending on etiology of bradycardia, pacemaker therapy could be indicated • AS- If all other sources of syncope are ruled out, AVR may be indicated if patient is a surgical candidate
Neurologic (<10%) • Seizure • Stroke/TIA • Subclavian steal	Seizure: lateral tongue biting (Sn 20-33%, Sp 96-100%), urinary/fecal incontinence (Sn 38%, Sp 57%), aura, postictal confusion Focal deficits: stroke, TIA Steal: syncope after arm exercise	• Seizure: EEG • Stroke: CT, MRI/MRA • Steal: UENI w/ Dopplers (specify for subclavian steal) • Carotid dopplers are of low clinical utility (changes management in <2% of patients) (JAHA 2014;3:e001063)	• Based on etiology, consider neurology consult and follow guideline-directed management & therapy

Cardiology

Severe Asymp. HTN & Emergency

DEFINITIONS, TRIAGE, AND MANAGEMENT: see *Outpatient CV Health* for workup (NEJM 2019;381:1843; HTN 2024)

- **Severe asymptomatic HTN** (HTN urgency): SBP ≥180 or DBP≥120 w/o evidence of end-organ damage (may have **mild headache**)
  - **Assess adherence** to prior rx before aggressively up-titrating regimen to avoid overcorrection of BPs & hypotension
  - **Assess causes** before tx; commonly due to pain, anxiety, urine retention, meds (e.g. steroids), OSA, nausea, withdrawal, etc.
- **Hypertensive emergency**: SBP ≥180 or DBP≥120 w/ evidence of end-organ damage
  - End-organ damage: Neuro: HTN encephalopathy (severe HA, seizure, AMS), PRES, TIA, CVA (SAH, ICH); Retinopathy: papilledema, hemorrhage; Resp/CV: flash pulmonary edema, MI, angina, Ao dissection; Heme: MAHA; Renal: AKI, hematuria

	Severe Asymp. HTN (JHM 2018;13:860)	Hypertensive Emergency
Triage location	Floor vs outpatient mgmt (with close follow up) (HTN 2024)	Floor vs ICU (ICU if needs arterial line, antihypertensive gtt, or if severe end-organ damage)
Correction time course	↓BP no more than 25-30% over hrs-days; then to goal as outpt. If hospitalized for non-cardiac reason, **worse** outcomes w/ intensifying anti-HTN during admission (JAMA IM 2021;181:345-352)	MAP ↓ by 10-20% in 1st hr, further 5-15% over next 23 hrs. Reduce BP by max 25% within first hour, and to no lower than 160/100 within 2-6h; reduce to normal range over 24-48h
Route of medication administration	PO meds; avoid IV or high-dose meds (risk for AKI, stroke, MI d/t hypoperfusion)	Start with short-acting, titratable IV agents; transition to PO agents for floor/discharge
Suggested meds (see below for dosing)	PO: start captopril, labetalol >> hydralazine (unpredict., reflex tachy) & convert to long-acting before discharge OR start long-acting agents	IV: labetalol >> hydralazine (high risk of overcorrection) Topical: nitro paste or patch (may be used on the floor) Drips: see below

Disease Process-Specific Recommendations for Hypertensive Emergency		
	BP Goal	**Suggested Medications**
ACS	SBP <140 w/in 1h; keep DBP >60	**Nitro (topical, gtt)**, esmolol > labetalol, nicardipine/clevidipine. *No BB if LV failure w/ pulm edema, HR <60, SBP <100, shock, high-grade HB. Judicious nitro if RVMI. No nitroprusside (cor steal) or hydral (ischemia).*
Acute pulm edema	SBP <140 w/in 1h	**Nitro (topical, gtt)**, nitroprusside, nicard/clevid; No BBs.
Aortic dissection	Fast!-SBP <120 & HR <60 w/in 20min	**IV BB** (**labetalol, esmolol**), followed by vasodilator (nicardipine/clevidipine)
Ischemic stroke	<185/110 if lysis; <220/120 if no lysis or organ damage (permissive HTN)	Labetalol, Nicardipine, Clevidipine
Hemorrhagic stroke	SBP >220, reduce by 25%. If SBP 180-220, target reduction to 140-160	
PRES	Immediate MAP decline 20%–25%	

Antihypertensive Dosing – ICU				
Agent	**Dosing**	**Onset**	**Duration**	**Indications**
Esmolol (IV)	500µg/kg load (given over 1 min) + infusion 25-50µg/kg/min; then adjust by 25µg/kg/min q10-20min up to 300µg/kg/min	<1min	10-20min	Ao dissection, CAD, peri-op HTN, *avoid* in ADHF
Labetalol (IV)	10-20 mg load + 20-80mg bolus q10min **or** 20 mg load + 0.5-2mg/min infusion, adjust to goal, max dose 300 mg	<5min	3-6h	Ao dissection, CVA, *avoid in ADHF/pulm edema*
Nitroprusside (IV)	0.25-2µg/kg/min (dose limit to avoid cyanide toxicity), temporarily (<10min) can use up to max 10µg/kg/min	<1min	<2min	AS/LVSD and HF; *avoid in ACS/CAD or CVA*
Nitroglycerin (IV)	Start 10-30µg/min, titrate by 10-20µg/min q5-10min; max 400 µg/min (if no response by 200 µg/min = non-responder)	2-5min	5-10min	ACS, flash pulm edema (FPE)
Nicardipine (IV)	Start at 5mg/h; ↑ by 2.5mg/h q5-15min; max 15mg/h	5-10min	15min-4h	SAH, CVA, Ao diss, FPE
Clevidipine (IV)	Start at 1-2mg/h; most respond to 4-6mg/h, max 21mg/h	2-4min	5-15min	SAH, CVA, Ao diss, FPE

Antihypertensive Dosing – Floor					
Agent		**Dosing**	**Onset**	**Duration**	**Indications**
Labetalol	**IV**	5-20mg, followed by 10-80mg q10min prn, then use PO	5-10min	3-6h	Ao dissection, CVA; *avoid in ADHF / FPE*
	PO	Start 100mg q8-q12h (max: 2400mg/d)	20min	8-12h	
Hydralazine	**IV**	5-20mg q15-30min until effect seen, then PO, **careful of unpredictable response** (10-40mg IM if no access)	10-20min	1-4h	Eclampsia
	PO	Start 10mg q6h, inc by 10-25mg/dose q2-5d	20-30min	~8h	
Captopril (PO)		12.5-25mg q8h (NOT TID)	30-90min	6-8h	Scleroderma renal crisis
Lisinopril (PO)		Initial 2.5-5mg qd. Inc 10mg q2w to max 40mg qd. (Can use ARB if ACEi intolerance)	1h	24h	T2DM, proteinuria, HF
Amlodipine (PO)		Initial 2.5-5mg qd. Inc 2.5mg q7d to max 10mg qd. **Requires few days to take effect**	24-48h	24h	No specific indications
Nifedipine (PO)		10-30mg TID. May cause pronounced vasodilation/orthostasis	20min	6-8h	Post-partum HTN
HCTZ (PO)		Initial 12.5mg qd (max: 50mg qd, doses >25 mg a/w ↑electrolyte derangements)	2h	6-12h	CKD1-3a/b
Isosorbide dinitrate (PO)		Initial 5-20mg 2-3 times/d (dose TID not q8h for nitrate holiday). Mononitrate = long-acting	1h	~8h	Angina, ESRD, HF

Cardiology

Peripheral Artery Disease

Overview (2024 Guideline)

- Definition: arterial stenosis or occlusion causing an imbalance of blood flow relative to muscular metabolism (legs > arms)
- Epidemiology: **smoking, DM**, HTN, HLD, ↑age (20% prevalence >70y) (Lancet 2013;382:1329)

Clinical Presentation and Diagnosis

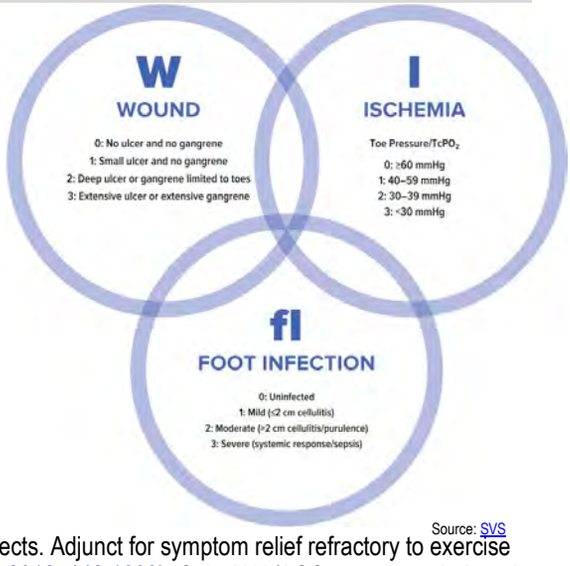
- Symptoms: (Circ 2006;113:e463)
  - **Classic claudication** (10-35%) - reproducible exertional pain (buttock, thigh, calf, ankle), relieved by rest (differentiate from pseudo-claudication from spinal stenosis); **atypical leg pain** (most common, 40-50%); **asymptomatic (20-50%).**
  - **Threatened limb** (1-2%): pain at rest (improved w/ hanging feet off bed or walking), ulcers at pressure points, dry gangrene
  - Rutherford classification: clinical criteria +/- objective data from treadmill test and ankle BP (JVascSurg;1997;26:517)
- Exam: arterial bruit, **↓peripheral pulses** (palpation, Doppler), ↓cap refill, pallor on elevation, ulcers, atrophic changes, ↓hair
- Diagnostics:
  - ABI: Doppler US. Ratio of DP/PT (higher value) SBP to brachial SBP.
    - Abnormal: **≤0.9** (95% Sn and 100% Sp for detecting arteriogram-positive lesions with ≥50% stenosis). ABI ≥1.40 suggests ↓compressibility usually due to ↑calcifications (e.g., elderly, DM, ESRD)
    - If ABI ≥1.40, a toe brachial index can be used for diagnosis
  - If ABI abnormal: obtain segmental ABI with pulse volume recordings (**PVR**) to localize disease
  - Exercise testing: if high suspicion for PAD & normal resting ABIs
  - CTA (with distal run off), MRA, or angiography: if considering endovascular or surgical revascularization

ABI	Interpretation
>1.40	Noncompressible vessel (not interpretable). Due to extra-luminal vessel calcification (Monckeberg)
1.00 - 1.40	Normal
0.91 - 0.99	Borderline
0.41 - 0.90	Mild to moderate PAD
0.00 - 0.40	Severe PAD

Rutherford Grade	Rutherford Stage	Clinical Description
0	0	Asymptomatic
I	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
II	4	Rest Pain
III	5	Minor tissue loss
	6	Major tissue loss

Treatment

- Optimize CV risk factors (e.g., HTN, DM, HLD, weight loss), high-intensity statin, smoking cessation
- Formal exercise program
  - CLEVER-RCT: supervised exercise therapy is at least as effective as stenting (JACC 2015;12:2055)
  - ERASE-RCT: supervised exercise therapy + revascularization > exercise alone (JAMA 2015;314:1936)
- Ischemic ulcers: wound care, may also need revascularization for appropriate healing depending on ABI
- Anti-platelets: For secondary prevention. If symptomatic, **ASA** 75-162mg qd *or* **clopidogrel** 75mg qd: ↓MI, CVA, vascular death (NEJM 2017;376:32).If asymptomatic, consider ASA 81mg. **Avoid DAPT** (NEJM 2006;354:1706) unless clinically indicated, usually post-revascularization. Review w/ clinical decision making algorithm (JACC 2018;71:2450).
- Anti-coagulation: rivaroxaban 2.5mg BID + ASA: ↓major adverse cardiac & limb events vs ASA alone (Lancet 2018;391:219). Caution as ↑major bleeding, but no ↑fatal bleeding in pts w/ stable PAD in study



Source: SVS

- Cilostazol: Start 100mg BID. PDE3 inhibitor w/ vasodilatory and anti-platelet effects. Adjunct for symptom relief refractory to exercise therapy/smoking cessation. Use in combination with ASA or anti platelet (Chest 2012; 142:1608). Only AHA/ACC recommended med to ↑exercise capacity (Circ 2017;135:e686). Contraindicated in HF
- Endovascular repair (angioplasty vs stent) if threatened limb and/or severe symptoms refractory to medical management. Assess benefit of revascularization vs amputation with SVS WIfI score, above (JVS 2014; 59:P220-234)

Acute Limb Ischemia (BMJ 2000;320:764)

- Sudden decrease in limb perfusion threatening viability. **Emergency** - consult Vascular Surgery and Vascular Medicine STAT
  - *Viable*: no immediate threat of tissue loss; audible arterial Doppler signal, intact motor/sensory
  - *Threatened*: salvage requires prompt intervention; no audible arterial Doppler signal, motor or sensory deficits
- Etiologies: embolic (e.g., AF, endocarditis) > thrombosis (e.g., atherosclerosis, APLAS, HITT), trauma, connective tissue disease
- Precipitating factors: dehydration, HoTN, abnormal posture (i.e. kneeling), malignancy, hyperviscosity, hypercoagulability
- Presentation: (6Ps) **P**ain, **P**oikilothermia, **P**allor, **P**ulselessness, **P**aresthesia (unable to sense light touch), **P**aralysis
- Diagnosis: pulse (w/ Doppler) + neuro checks; angiography (CTA w/ run-off or arteriography)
- Treatment: anti-coagulation ± IA lytic; endovascular repair vs thrombectomy; continuous prostaglandin infusion
- After treatment, monitor for reperfusion acidosis, hyper-K, myoglobinemia (ATN), & compartment syndrome

Will Pohlman

Cardiology

Cardio-Oncology

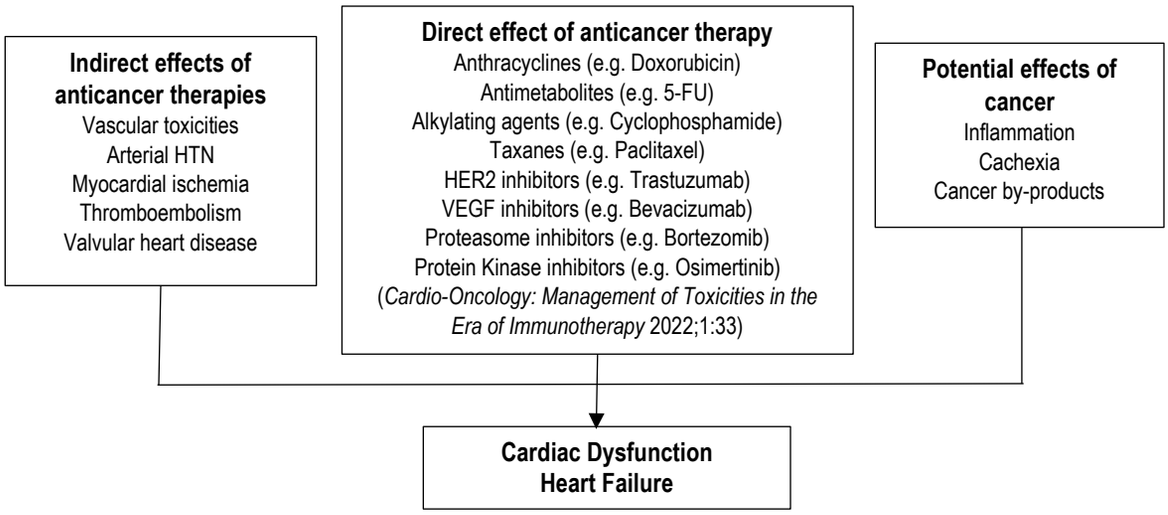
OVERVIEW (JACC 2017;70:2536; JACC 2017:70:2552)

Chemotherapy cardiovascular toxicity: includes many different presentations including cardiomyopathy, ischemia, vasospasm (5-FU), atherosclerosis, HTN, myocarditis (ICI), pericardial disease (chemo or XRT), thromboembolism, QT prolongation, and arrhythmias.

Risk factors: pre-existing CV disease or known cardiovascular risk factors (DM, HLD), extremes of age, female sex
Diagnosis: TTE (compared to baseline), ECG, TnT (↑correlates to adverse cardiac events post-chemo), MRI/PET/biopsy if suspect ICI myocarditis (Lancet Onc 2018;19:e447)
Prevention: consider BB/ACEi if EF <50%, EF drop >10% or abnl TnT (Am J Clin Onc 2018;41:909), ARB>BB protection against EF decline in early breast Ca with adjuvant tx (EHJ 2016;37:1671); consider pre-emptive vasodilators/serial ECGs in 5-FU + capecitabine
Screening/monitoring:

- TTE surveillance schedule depends on therapy & baseline cardiac risk; ranges from q3-6mo with long-term risk >10y. Additional imaging modalities should be used in patients with cardiac risk factors (Circulation 2023;48:1271)
- Monitor weekly BP in first cycle, then q2-3 weeks on therapy
- Certain therapies with well-studied CV risk (i.e., anthracyclines, Trastuzumab, radiation) have guidelines to direct CV monitoring, however, most do not and proper CV monitoring is an ongoing area of investigation. Pragmatic surveillance strategies have been proposed and may be useful managing a cancer patient with a new cardiac symptom/condition (JAHA 2020;9:e018403))

Treatment: Optimize preventative CV health (e.g., lipids, DM, blood pressure, etc.) and standard HF and ischemic work up/management (generally, ASA if plt>10k, DAPT if plt>30k). Cessation of chemotherapy often last resort (multi-disciplinary conversation)



IMMUNE CHECKPOINT INHIBITORS AND RADIATION

Examples: Ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab

- **ICI Cardiac Toxicity *(see ICI)***: Myocarditis (best studied), also been associated with Takotsubo syndrome, ACS, arrhythmias, pericardial disease, fulminant myocarditis (RF = combo therapy)
  - **Dx**: troponins, EKG, TTE, cMRI (Sn 50%), endomyocardial bx (lymphohistiocytic inflammatory infiltrate, T cells in HPF)
  - **Tx**: stop ICI; pulse-dose steroids (e.g., 1g IV methylprednisolone x 3-5d) → steroid taper; with cardiology/oncology team can consider further immunosuppressive agents
- **Radiation:** Can cause CAD (up to 85%), pericardial disease (6-30%), CM (up to 10%), valvular abnormalities, PVD, arrhythmias, autonomic dysfunction, can occur 10-15 years later, many RF including dosage, metabolic RF
  - **Screening:** Recommend stress testing within 5-10 years after chest radiation

ADDITIONAL COMMON CARDIOTOXIC THERAPIES

- **Anthracyclines** (Doxorubicin, idarubicin, epirubicin, daunorubicin): Best characterized cardiotoxicity; HF in dose-dependent manner; LV dysfunction (5-23%), irreversible damage; should perform baseline cardiac imaging (TTE) prior to tx
- **Taxanes** (paclitaxel, docetaxel): Conduction abnormalities (bradycardia, heart block); potentiate toxicity of anthracyclines
- **Alkylating agents**:
  - **Cyclophosphamide**: Cardiomyopathy associated with high-dose protocols (not cumulative dose); hemorrhagic myocarditis
  - **Ifosfamide**: Arrhythmias, ST-T changes, HF (dose-related)
  - **Cisplatin**: SVT, bradycardia, ST-T changes, LBBB, ACS, iCM. Peripheral vascular: Raynaud, HTN, CVAs
- **5-FU**: Myocardial infarction, vasospastic angina
- **Monoclonal Abs**:
  - **Trastuzumab (HER2)**: 2.1% risk of ↓LV dysfunction, resolves once stopped; TTE q3months
  - **Bevacizumab (VEGF)**: HTN, 3-fold increase in arterial thromboembolic events
- **Protein kinase inhibitors**:
  - **Osimertinib, mobocertinib (EGFRi)**: CMP, QTc prolongation
  - **Sorafenib, sunitinib (multi TKI)**: HTN, HF, conduction abnormalities
  - **Ibrutinib, zanubrutinib (Bruton TKI)**: SVT, VT, HF, HTN

Proteasome inhibitors (carfilzomib, bortezomib): HF, pHTN, MI

Epidemiology of Cardiovascular Disease

Overview: Leading cause of death in developed countries; CVD includes: CAD, CVA, PAD, aortic disease

Risk Factors:

- Non-modifiable: Age (each decade confers 2x ↑ risk from prior), Sex (F with ~20% ↓ risk than M, though risk ↑ 3x in F post-menopause), FHx premature ASCVD (1st degree relative w/ ASCVD before 55y M or 65y F), elevated lipoprotein(a)
- Modifiable: HTN, HLD (↑ Total, LDL-C, ApoB, Non-HDL, Lp(a), or TG; ↓ HDL), DM, CKD, obesity, smoking (esp. current), exercise, alcohol, diet, psychosocial stress (chronic + acute), chronic inflammation (CRP best biomarker), mediastinal radiation, HIV

Aspirin for CVD Prevention

Primary prevention:

- 2019 ACC/AHA 1° prevention guidelines: **No routine rx; might consider low-dose ASA for 1° prevention in select pts 40-70y at ↑ ASCVD risk & not at ↑ bleeding risk; avoid ASA for 1° prevention in pts >70y** (Circ 2019;140:e596)
- Key trials: ASCEND (NEJM 2018;379:1529, pts >40y w/ DM), ARRIVE (Lancet 2018;392:1036, pts w/ multiple non-DM CVD RFs), & ASPREE (NEJM 2018;379:1519, pts >70y [>65y if Black/Hispanic]): low-dose ASA either w/out sig CV benefit or w/ CV benefit counterbalanced by ↑ risk of major bleeding
- CAC >100 or >75th percentile per MESA calculator (Circ. 2020;141:1541–1553): Consider low-dose ASA (JAMA Cardiol 2021;6(2):179–187). CAC >1000, very high risk for ASCVD, requires aggressive primary prevention including low dose ASA (Circulation. 2021;143:1571–1583).

Secondary prevention: In pts w/ stable CVD, low-dose ASA ↓ incidence of adverse CV events and all-cause mortality (AmJMed 2008;121;43)

Outpatient Blood Pressure Screening and Management

2017 ACC/AHA guidelines (HTN 2018;71:1261):

- Definition: HTN = SBP >129 or DBP >79 independent of kidney function or age; US prevalence 46%
- Method: 2 checks >1w apart, sitting 5min with arm at heart level, cuff bladder 80% length & 40% width of arm circumference
  - **24h ambulatory SBPs** show greater association w/ all-cause mortality than clinic BPs. Patient log here.
- Categories: *Normal*: <120/(and)<80; *Elevated*: 120-129/(and)<80; *Stage 1 HTN*; 130-139/(or)80-89; *Stage 2 HTN*: >140/(or)>90

Initial Workup: BMP, Ua, Ualb/Cr ratio, CBC, fasting glucose, TSH, lipids, baseline ECG, 10-yr ASCVD risk, consider TTE (eval for LVH)

2° HTN: *targeted approach to workup,* consider the following indications (HTN 2018;72:e53):

- Resistant HTN (not controlled on 3+ agents [at least one diuretic]) OR Severe HTN (controlled on 4+ agents [at least one diuretic])
- Acute rise in blood pressure in a previously well-controlled patient, esp. DBP
- Age <30y w/o risk factors (e.g. obesity, FHx)
- HTN with suggestive electrolyte disorders (hypoK, metabolic acidosis)
- Malignant OR Accelerated HTN (severe HTN presenting with clinical or laboratory signs of end-organ damage)

Secondary Causes of HTN		
Cause	**Clinical Clues**	**Work-up**
Medications/Drugs (use or withdrawal)	NSAIDs, OTC decongestants, OCPs, anti-depressants, corticosteroids, sudden d/c of anti-HTN meds (i.e., clonidine)	Thorough history
OSA	Obesity, snoring, smoking	Sleep study
Renal disease	Elevated Cr, protein/blood on UA	See *AKI* and *CKD*
Primary aldosteronism	**Hypokalemia**, hypernatremia, adrenal incidentaloma, FHx	Plasma aldo:renin activity; measure together in morning (~8AM), after pt awake for >2h, seated for >5 minutes; **high rates of underdiagnosis and undertreatment**
Renal artery stenosis	>50% rise in Cr after ACE/ARB initiation; lateralizing abdominal bruit; severe HTN in s/o atrophic/asymmetric kidneys, or diffuse atherosclerosis/FMD	If intervention likely to be pursued, begin with Duplex Doppler US (Sn 85%, Sp 92%) → if stenosis (ARAS>50%) or ambiguous results, consider angio
Rare: pheochromocytoma, Cushing's disease, hyper/hypothyroidism, hyperparathyroidism, aortic coarctation, ADPKD		

Lifestyle Counseling (HTN 2018;71:1261)		
Intervention	**Approach**	**SBP impact in pts w/ HTN**
Exercise	Aerobic: 90–150 min/wk at 65-75% HR reserve	↓5-8mmHg
Exercise	Dynamic resistance (see guidelines for program specs)	↓4mmHg
Exercise	Isometric resistance (see guidelines for program specs)	↓5mmHg
Weight loss	Weight reduction in overweight/obese adults	↓1mmHg for every 1kg of weight lost
Diet (DASH)	↑veg, fruit, whole grain, lean meat; ↓sweets, red meat	↓11mmHg
Sodium	Consume <1.5g/day	↓5-6mmHg
Potassium	Consume 3.5-5g/day	↓4-5mmHg
Alcohol	Limit consumption to <1/2 standard drink/d in F/M	↓4mmHg

Medical Management (HTN 2018;71:1261)	
When to Treat	**Stage II HTN** or **Stage I *if*:** clinical CVD, DM2, CKD, or ASCVD ≥10%
Target BP	<130/80
Choice of Agent	First-line: thiazides (chlorthalidone may not be > HCTZ, ↑SEs (JAMA IM 2020;180:542)), ACEi/ARB, CCB Other: βB, hydralazine, isosorbide, clonidine, α-blockers (e.g. doxazosin), minoxidil (rare)
Compelling Indications	DM2: ACEi/ARB (if proteinuria) HF: βB, ACEi/ARB, diuretic, spiro CKD: ACEi/ARB CAD: βB, ACEi/ARB Pregnancy: labetalol, CCB
Monitoring	Follow-up eval for BP response/adherence at monthly intervals until BP controlled Labs: check BMP/Mg if starting ACEi/ARB or diuretic, 2-4w after initiation, then yearly or w/ Δdose
Important Trials Re: BP goals	SPRINT (NEJM 2015;373:2103): SBP goal <120 vs 135-139 ↓CVD events & all-cause mortality in high-risk pts, but ↑non-orthostatic hypotension, syncope, electrolyte abnormalities, & AKI ACCORD BP (NEJM 2010;362:1575): in pts w/ DM, no CV mortality benefit a/w SBP goal <120 vs <140

Outpatient Cholesterol Screening and Management

2018-9 ACC/AHA guidelines (Circ 2018;139:e1082, Circ 2019;140e596)

- Screening:
  - Check a lipid panel in adults ≥20y to establish baseline LDL-C and estimate ASCVD risk
  - Measurement of apoB and Lp(a) may confer nuance to risk estimation; approaches are evolving (JAMA Cardiol 2019;4(12):1287; JAMA 2021;326(4);352)
- Methods:
  - Fasting: *not routinely recommended*; consider if non-fasting TG >400 or pt has FHx premature ASCVD or genetic hyperlipidemia
  - Low LDL-C: If LDL-C <70 *and precise measurement warranted*, measure direct/modified LDL-C (Friedewald formula less accurate with decreasing LDL-C)
- **Familial hypercholesterolemia (FH)**: Heterogeneous diagnostic criteria, typically combo of suggestive clinical (premature CVD, tendon xanthomas), lab (LDL-C ↑↑), genetic (LDLR, APOB, PCSK9), and FHx (strong FHx premature CVD) findings
- Common 2° causes of dyslipidemia: **Diet** (weight gain, anorexia, alcohol, diet rich in trans/sat fats or refined carbs), **drugs** (orals estrogens, glucocorticoids, diuretics, anabolic steroids, amiodarone, tamoxifen, raloxifene), **diseases** (nephrotic syndrome, chronic renal failure, biliary obstruction), **disordered metabolism** (hypothyroid, obesity, pregnancy, poorly-controlled DM)
- See indications for/approaches to rx below; *statin therapy is the cornerstone of med rx*, should be added to maximally tolerated effect before reaching for secondary meds
- Lipid monitoring:
  - Yearly if pt at goal & compliant
  - Assess 4-12w after statin initiation or dose change, repeat q3-12mo as needed

Lifestyle Counseling (Circ 2018;139:e1082,Circ 2019;140e596)	
Intervention	**Approach**
Diet	Emphasize: veg, fruit, whole grain, legume, healthy protein sources (low-fat dairy/poultry, fish, nuts), non-tropical veg oils, unsat fats Limit: sweets, refined carbs, processed/red meats, trans/sat fats, sweetened beverages
Weight control	Weight loss in overweight/obese pts; reasonable to track risk with BMI, waist circumference measurement
Exercise	Target: aerobic, 3-4 sessions/wk, ~ 40min/session, moderate-to-vigorous intensity. At least total/week of 150min of moderate-intensity or 75min of vigorous-intensity physical activity. Decrease sedentary behavior
Tobacco	Screen for use at every visit and assist with quitting/reduction when possible

Indications for Statin Therapy		
	ASCVD Risk Estimator Established pooled cohort 10yr risk calculator for 1° prevention Ages 40-79y Currently in guidelines, likely to be replaced by PREVENT	PREVENT Score New 10yr and 30yr risk calculator for 1° prevention Ages 30-79y Race free. Includes eGFR/UACR, BMI, A1c, and zip code (proxy for SDH)
Clinical ASCVD, <75y	(e.g. CHD, TIA/stroke/CAS, PAD, TAA/AAA) Maximally-tolerated statin to reduce LDL-C by ≥50%	
LDL-C ≥190, 20-75y	Maximally-tolerated statin to reduce LDL-C by ≥50%	
Diabetes (age 40-75)	Moderate-intensity statin; consider high-intensity statin for ASCVD risk >20%, multiple ASCVD RFs to reduce LDL-C by ≥50%	
Age 40-75 w/o above	(10 yr ASCVD) Low risk <5%: lifestyle changes Borderline risk 5-7.5%: consider mod-intensity statin based on risk-enhancers* Intermediate risk 7.5-20%: statin to ↓LDL-C ≥30-49%, CAC may help decision High risk >20%: statin to ↓LDL-C ≥50%	

*ASCVD risk enhancers: FHx premature ASCVD, LDL-C ≥160, CKD, premature menopause (age <40), hypertensive disorders or pregnancy (eg pre-eclampsia), metabolic syndrome, inflammatory dz (RA, HIV, SLE, psoriasis), ethnicity (South Asian), TG ≥175, hs-CRP ≥2, Lp(a) ≥50, apoB ≥130, ABI <0.9

*Coronary artery calcium (CAC) score: 0 favors no statin in intermediate risk in absence of DM, active smoking, or early FHx; 1-99 favors statin therapy; CAC 100+, initiate statin

Common Medications					
Medication	**Mechanism**	**Indication**	**% ↓ in LDL-C**	**Effect on CV outcomes**	**Adverse effects**
Statins*	HMG-CoA reductase inhibitors	1st-line therapy for 1° & 2°prevention	20-60% LDL-C reduction	1° & 2°prevention, ↓**CV events** (ARR 1.1%, NNT 91, HOPE-3)	Myopathy (↓↓prevalent in RCTs vs "practice"), ↑LFTs, memory loss & confusion
Ezetimibe (10mg qd)	↓intestinal cholesterol absorption	- Statin-intolerant - LDL-C >70 w/ CVD or <50% ↓LDL-C w/o CVD on max-tolerated statin	Ezetimibe + statin therapy ↓ LDL-C by ~23%	Ezetimibe + statin ↓**CV events** (ARR 2%, NNT 50, IMPROVE-IT)	Mild ↑LFTs (usually w/ statin)
PCSK9 inhibitors (alirocumab, evolocumab)	Block degradation of LDL-R on hepatocyte surface	High risk pts w/ CVD & LDL-C >70 on statin + ezetimibe; approved for use in familial hypercholesterolemia	38-72% reduction; ~60% in pts on statin therapy	Evolocumab + statin ↓**CV events** (ARR 1.5%, NNT 67 at 48w, FOURIER); alirocumab + statin ↓**CV events** (ARR 1.6%, ODYSSEY)	Uncommon; mainly injection site reactions Cost: 150k/QALY
O3FAs (e.g. Vascepa [EPA])	Incorporate into phospholipids	Severe hyperTG, hyper TG despite statin, CVD prevention	↓TG ≥30% with no Δ in LDL	EPA + statin ↓**CV events** (ARR 4.8%, NNT 21, REDUCE-IT)	Interaction (e.g. warfarin), GI sx
Note: if patient has concomitant **severe hypertriglyceridemia (TG >886 mg/dL)**, then also start **fenofibrate** (many formulations)					

Statin Potency	
High-intensity (≥50% ↓LDL-C)	atorvastatin 40-80mg rosuvastatin 20-40mg
Mod-intensity (30-49% ↓LDL-C)	atorvastatin 10-20mg, rosuvastatin 5-10mg, simvastatin 20-40mg, pravastatin 40-80mg, lovastatin 40-80mg, pitavastatin 2-4mg
Low-intensity (<30% ↓LDL-C)	simvastatin 10mg, pravastatin 10-20mg, lovastatin 20mg

***Statin Properties**:
Biggest change in LDL: rosuvastatin > atorvastatin > simvastatin
Safest in CKD: atorvastatin, fluvastatin (no renal dose adj. required)
Safest in cirrhosis: pravastatin
HIV patients: pitavastatin (REPRIEVE)
Lowest rate of myopathy: pravastatin, fluvastatin
Least DDI: pravastatin, rosuvastatin, fluvastatin (no CYP450 metabol.)
Lower overall side effects: pravastatin, rosuvastatin (hydrophilic)
ACC Statin Intolerance Tool: to assess for muscle side effects

MANAGEMENT OF CHRONIC CORONARY DISEASE (CCD)

2023 ACC/AHA guidelines (Circulation. 2023;148:e9–e119)

- Definition: a) prior ACS event or revascularization b) impaired LV systolic function from ischemic cardiomyopathy c) medically managed stable angina +/- positive stress test d) angina from microvascular disease and coronary vasospasm, or e) ASCVD based on screening test (eg stress test, cCTA) or clinical judgement
- Evaluation: Yearly evaluation by cardiologist is recommended to assess for worsening of symptoms. Anatomic or ischemic evaluation in the absence of symptoms is not recommended.
- Medication:
  - **Lipid Lowering**: Goal ≥50% LDL reduction and/or LDL ≤ 70mg/dL (for very high risk clinical ASCVD), see above
    - No evidence for use of fish oil and omega-3 fatty acids/vitamins in reducing cardiovascular events.
  - **Anti-platelet**: ASA 81mg in all patients. See *Adjuncts to Revascularization* for post-stent anti-platelet therapies
  - **Beta-blocker**: Long term beta-blocker is indicated among individuals with prior MI <1 year, LVEF ≤40% regardless of prior MI; in patients with LVEF ≤50%, use of metoprolol succinate, carvedilol or bisoprolol is preferred.
    - Among CCD individuals with prior MI > 1 year and no history of LVEF≤50%, angina, arrhythmias or uncontrolled HTN, can consider discontinuation of long-term use (>1 year) of beta-blocker
    - No known benefit for beta-blockade among individuals with CCD without prior MI
  - **Anti-Hypertension**: Goal BP <130/<80; See *Outpatient Blood Pressure Screening and Maintenance* above
  - **Special populations**:
    - Patients with diabetes: SGLT2i or GLP-1 receptor agonist reduces risk of MACE
    - Patients with EF ≤40%: SGLT2i reduces risk of cardiovascular death and HF hospitalization.
    - Patients with overweight or obesity (BMI ≥27): GLP-1 receptor agonist, semaglutide over liraglutide
  - **Anti-anginal**: Beta blocker or calcium channel blocker as first line agents for symptom management, followed by long-acting nitrates, use ranolazine as 3rd line
- Lifestyle modification: See *Lifestyle Counseling* above

Cardiology

Anti-Arrhythmic Medications

Class	Name	Mechanism	Usage	Dosing	Side effects, Contraindications (CI)
IA	**Procainamide** (IV)	Na^+ channel blockade; conduction slowing; ↑action potential; also has Class III action	VT; AF, **especially in accessory bypass tracts (WPW)**	VT: 100mg q5min until total 500mg, wait 10min for distribution. Admin to arrhythmia control, HoTN or QRS inc. by 50% WPW: 20mg/min until total 17mg/kg (e.g., ~1h, BP q5min); then 2-6mg/min (in urgent situations, up to 50mg/min may be given to total dose ≤17 mg/kg)	HoTN, PVCs, VT, ↑QT, **drug-induced lupus (long term use)**, agranulocytosis, neg. inotropy. CI: CHB, AVB, SLE, TdP
	Disopyramide (PO)	Na^+ channel blockade; anticholinergic effects	**HOCM** (efficacy relates to negative inotropic effect), VT, AF, Aflutter	VT: if <50kg→load 200mg x1, then 100mg q6h; if >50kg→load 200mg x1, then 150mg q6h AF conversion: 200mg q4-6h AF prevention: 400-750mg, divide q6h (w/ BB/CCB) HOCM: 200mg q12h, CR form is oral	**Anticholinergic** side effects, **neg. inotropy,** HoTN, CI: ↑QTc, HFrEF
IB	Lidocaine (IV)*	Na^+ channel blockade; no effect on conduction; may ↓action potential	**VT, VT/VF arrest, polymorphic VT**	Load: bolus **1.0-1.5mg/kg**. May give additional 0.5-0.75 mg/kg IV push PRN q5-10min; total ≤3 mg/kg Maintenance: **1-4mg/min (30-50mcg/kg/min)**	Bradycardia, junctional arrhythmia, HoTN, angina, AMS, tremor, seizure, dysarthria, paresthesias, nausea, dizziness
	Mexiletine (PO)	PO analogue of lidocaine	**VT**	Load: 400mg x1 Maintenance: 200mg q8h	Tremor, nausea, dizziness, GI. CI: cardio shock, 2°/3° AVB
IC	**Flecainide** (PO)*	Na^+ channel blockade	**pAFib** ("pill in the pocket"), rarely ventricular arrhythmia	Pill in the pocket: 200mg (<70kg) or 300mg (>70kg). Max: qd Sinus rhythm maintenance: 50-150mg bid	**Ventricular arrhythmia** (↑risk if structural heart dz), neg. inotropy, dizziness. CI: HFrEF, IHD, ↑QTc, CrCl<50, liver dz
	Propafenone (PO)	Na^+ channel blockade; Some β1 blockade	Same as above	Pill in the pocket: 450mg(<70kg) or 600mg (>70kg). Max: once/24h. Start BB/CCB prior Sinus rhythm maintenance: 225-425 bid ER q12h	**Ventricular arrhythmia** (↑risk if structural heart dz), GI sx, dizzy. CI: IHD, HFrEF, LVH, ↑QTc
II	Esmolol (IV)	β1 antagonist. t 1/2 = 9min	Acute HR/BP control in **Ao dissection**, SVT	Load: 0.5-1mg/kg x1min Maintenance: 2-21mg/min IV (25-300mcg/kg/min)	Same as other β-blockers Atenolol is renally cleared (adjust if AKI)
	Atenolol (PO)*	β1 antagonist; 2x as potent as metoprolol	SVT, ACS, post-MI, CAD, HTN, HF	25-50mg qd (max: 100mg qd)	
	Propranolol (IV, PO)*	Non-selective βB	**Thyroid storm**, AoD, tremor, EV ppx, pheo, anxiety	IV: 0.5-1mg load→1-3mg every several hours PO: 120-320mg/d (based on indication)	Crosses BBB, may cause **AMS**. Less HoTN than β1 antagonists
	Nadolol (PO)*		**Variceal ppx**	20-80mg qd (max: 240mg)	AMS, HoTN
III	Amiodarone (IV/PO)	K^+ channel blockade, slows repol. Multiple effects incl class Ia, II, & IV. **Class II (i.e. βB) = fastest effect**	**SVT, VT, pulseless VT/VF, (off-label) AFib**	Pulseless VT/VF: **300mg IV** push, may repeat 150 mg IV push every 3-5min as needed WCT: - IV: **150mg x1** (repeat q10 min prn)→**1mg/min x6h (360mg)→0.5mg/min x18h (540mg)** - PO: total **8-10g** over days (200-400mg, BID-TID) - Maintenance: 100-200mg PO QD-BID AF: PO 8-10g over 2-4w	HoTN (IV), bradycardia, ↑QT. Long $t_{1/2}$ (58d). Systemic SEs w/ long-term use (check baseline PFTs, LFTs, TFTs). **Do NOT use for TdP, pre-excitation**. CI: ↑QTc, SSS, 2°/3° AVB, sx bradycardia, cardiogenic shock
	Sotalol (IV, PO)*	Nonselective β1/β2 antagonist, K+ channel blockade	**AFib, VT**	IV: 75mg q12h, may ↑dose by 37.5mg q3d (max: 300mg/d) PO: 80mg q12h, may ↑dose by 40mg q3d (max: 320mg/d). Adjust dosing interval in renal impairment	↑QT, typical effects of β-blockade; CI: CrCl <40, LVH, HFrEF, ↑QTc, hypoK
	Ibutilide (IV)	K+ channel blockade, prolongs action potential	**AFib, AFlutter**	>60kg: 1mg over 10min; can repeat x1 in 10min; <60kg: same except dose is 0.01mg/kg	↑QT, TdP, HA
	Dofetilide (PO)*		**AFib, AFlutter**, SVT	Initial dose 500mcg bid max Decrease dose by 50% if CrCl<60 or QT prolonged	↑QT; CI: thiazide, dolutegravir, trimethoprim, verapamil, hypoK, hypoMg, CrCl<20
IV	Diltiazem (IV, PO)	CCB→slows AV node conduction & phase II of cardiac action potential	**AFib, AFlutter**, SVT, MAT, angina, HTN	IV: 0.25mg/kg (≤25mg) q15min prn; gtt **5-15mg/h** PO: 120-320mg ER qd or ≤480mg/d IR q6h	↓ inotropy CI: SSS, bradycardia, 2°/3°AVB, VT, AF + WPW, HoTN, pulm edema, HFrEF (<40%), ADHF
	Verapamil (IV, PO)			IV infusion: 5-10mg, repeat q15-30min PRN (≤20-30mg); gtt 5-20mg/h if needed PO : 120-360mg ER qd or ≤480mg/d IR q8h	
Misc.	Digoxin (IV, PO)*	Na/K ATPase inhibition→Ca influx. AV node conduction suppression, ↑vagal tone, +inotrope	**AFib, Aflutter**, HFrEF, SVT	IV (initial): total dose 8-12mcg/kg IBW (≤0.75-1.5mg) 3 divided doses, 50% over 5min as 1st, then 25% for 2nd & 3rd, q6h. Follow with maintenance. Goal: 0.5-0.8 (HF), <1.2 (AF) Oral (maintenance): 0.125-0.25mg qd	Digoxin tox (>2ng/mL usually), N/V, visual disturbance, atrial tachycardia with AV block, PVCs, VT, VF. CI: VF
	Adenosine (IV)	AV node conduction slowing, coronary vasodilation	**Treating SVT** Differentiating re-entry SVT from a-fib/flutter/tach	IV (admin over 1-2sec, PIV): 6mg→12mg after 1-2min if ineffective, repeat x1 if needed, flush immediately. **Half dose** if patient using central line, or receiving carbamazepine or dipyridamole.	Arrhythmia, angina, HA, flushing, GI distress, dyspnea. CI: 2°/3° AVB, SSS, sx brady, lung dz, asthma, s/p OHT

*Renal dosing required

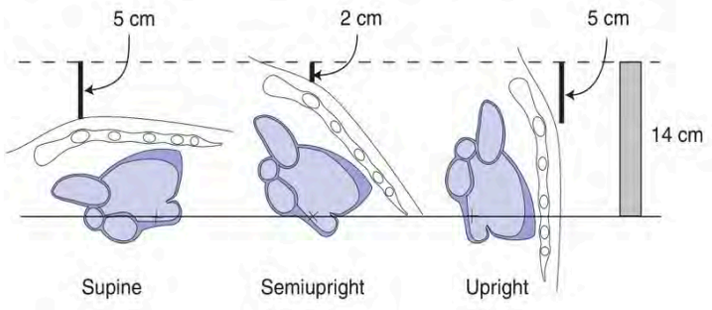
Brief Physical Exam Tips (McGee 2021)

	Pathophysiology	Tips for measurement	Sens/Spec & Likelihood Ratios	Diagnosis
JVD	Jugular vein is a central vein that is contiguous with the right atrium and act as a proxy for right atrial pressure	Angle changes measurement (see below); veins have respiratory variation & rise w/ hepatojugular reflex; nonpalpable. Add 5cm to approximate RAP; Reported in cm H2O	For measured CVP >8cm: Sn 47-92%, Sp 83-96%, +LR 8.9, -LR 0.3. Preop JVD +LR 11.3 for postop edema/+LR 9.4 for postop MI if no addl mgmt	Elevated in HF, tension PTX, tamponade, SVC syndrome, tricuspid stenosis and large CV waves in TR
S3	"Sloshing" of blood as it hits compliant ventricular wall. Occurs after S2; Early to middle diastolic sound	Heard best with bell at apex in left lateral decubitus	For EF <30%: Sn 68-78%, Sp 80-88%; +LR 4.1, -LR 0.3	Associated with HF; can be physiological in younger patients
S4	Flow of blood from atrial kick into stiff ventricular wall; late diastolic heart sound, right before S1	Heard best with bell at apex in L lat decubitus. Longer interval b/w S4/S1 → poorer prognosis	For elevated L heart filling pressure: Sn 35-71%, Sp 50-70%	A/w LVH, AMI, cardiomyopathy; can be normal in older adults; Cannot have in AF (no atrial kick)
Peripheral edema	Occurs when capillary hydrostatic pressure overwhelms ability of lymphatics to drain fluid from the instertitum; the lymphatic valves fail and the lymphatic vessels dilate.	+1 = 2mm depression, quick rebound +2 = 3-4 mm depression, quick rebound +3 = 5-6 mm depression, rebound <1min +4 = 8mm+ of depression, rebound 2-3min Measure in dependent area (i.e. sacrum for bedbound pts) and assess how far up extends	For elevated L heart filling pressure: Sn 10% Sp 93-96%, nonsignificant LR	Volume overload
RV heave	An indiciation of RV (or, rarely, LA) enlargement	Felt best over left parasternal region; if heel of hand rises with systole, there is heave	Limited; for pHTN, Sn 42%/Sp84%, nonsig LR	RV enlargement (incl pHTN, RV volume overload), or MR, rarely LA enlargement
AS murmur	Turbulent flow across stenotic AV; as severity increases & ejection takes longer, murmur becomes later & diminishes S2	Loudest R 2nd intercostal space, radiates to R carotid 1st as severity increases	For mild or worse AS: Sn 79-90%, Sp 85-87%, +LR 10.5, -LR 0.1. For severe AS Sn 83-98%, Sp 71-76%, +LR 3.5, -LR 0.1	Aortic stenosis; DDx increased Ao flow without obstruction (anemia, fever, pregnancy, nonobstructing calcification)

JVP Measurement Pearls

EJV is a good proxy for IJV in most patients; good reliability for discriminating high from low CVP (Arch Intern Med 2006;166:2132, Chest 2011;139:95)

Distance from sternal angle to right atrium is variable between patients and across positions (JGIM 2002;17:852 median 5 cm at 0°, 8 cm at 30°, 10 cm at 60°); interpret JVP in clinical context and trend while intervening on volume status (**McGee 2021**)



Sonographic JVP when bedside JVP difficult to visualize; correlates well with right atrial pressure (Ann Intern Med 2022;175:344, JASE 2023;36:278). Lay patient 30° - 45°, scan with vascular probe in short-axis just above the clavicle to find IJV and CA and slide cranially to find the IJV meniscus, then usual JVP calculation. Alternatively, if the IJV is distended (> carotid) with minimal pulsation just above the clavicle at 45°, can call JVD (JASE 2023;36:278). Easy rules: if IJ > carotid in short axis at 90°, rules in elevated RAP. If IJ < carotid in short axis at 30°, rules out elevated RAP

Cardiac Telemetry: Running the "Tele"

Step 1: Locate the name of the desired patient on the telemetry monitor and select their telemetry strip.
Step 2: Once on patient's telemetry strip, select "**Patient Data**."
Step 3: Click "**Event Review**" which will show you any abnormal events the patient had since being placed on telemetry. From this list, click the desired episode of choice.
Step 4: After clicking on the desired event, you will have multiple options to choose from:

- Events: events sorted in reverse chronological order (e.g. runs of NSVT, bradycardia)
- FD Strip: telemetry strip for a **specific moment** in time
- FD Page: global view useful in **identifying abrupt changes** that can be zoomed in on using the FD Strip view
- Graphic Trends: graphic view of **HR trends** over time
- Calipers: interactive calipers used to **calculate intervals** on telemetry strip

While a patient is on telemetry, review indication daily and discontinue if not using monitoring for clinical decision-making (refer to AHA Guidelines for appropriate use of hospital telemetry)

Pulmonary & Critical Care

Respiratory Distress

Respiratory distress is a constellation of symptoms that portends impending respiratory collapse. It is different from **dyspnea**, which is the subjective sensation of shortness of breath. Key symptoms of **respiratory distress** are:

- Tachypnea (go look at the patient and measure yourself. RR ≥20)
- Cyanosis (typically SpO_2 <80%)
- ↑WOB (nose flaring, retractions, grunting, tripod-ing, diaphoresis)
- Obstruction (wheezing, stridor)

Approach

1) **Confirm code status**
2) **Low threshold to call Rapid Response for assistance**
3) **Assess airway, breathing, circulation & confirm access**
   - o **Place on supplemental O_2**: NRB to start, can always wean later
   - o **Red flags (RICU STAT)**: Inability to protect airway due to AMS, pooling secretions, hemoptysis, life-threatening hypoxemia despite supplemental O_2 (SpO_2 <80%, PaO_2 <55mmHg), severe hypercapnia despite BiPAP, tiring out (↑WOB, progressive hypercapnia), RR >35
   - o **Temporize**: suction, head-tilt chin lift (preferred if no concern for C-spine injury) vs jaw-thrust to open airway, bag-mask ventilation (enough volume to see chest rise, no more than 8-10cc/kg or 5-6cc/kg during CPR; 8-10 breaths/min). If use of bag-mask will not be brief & pt unresponsive, consider OP airway prior to intubation
4) **Initial workup**:
   - o **CXR** (order STAT, must call x**6-3050**): look for new infiltrate (aspiration, PNA), pulmonary edema, lobar collapse (mucus plug), PTX. For read, call **x4-1533.** If nl, consider ischemia, PE, acidosis
   - o **ABG**: worrisome if $PaCO_2$ >45mmHg (*poor ventilation*), PaO_2 <60mmHg (*poor oxygenation*), pH <7.25. MD or RT can obtain.
   - o **Labs**: VBG (& ABG if possible, correlate to VBG. Widened A-a gradient >20 = abnormal gas exchange vs nl <20 = global hypoventilation), hs-Trop, NT-proBNP, lactate, BMP, CBC
   - o **Additional studies based on clinical suspicion**: CT-PE (if stable to travel), TTE (acute valvular dz, RV strain), US (PTX/effusion)

Dyspnea DDx

- CV: MI, HF, VHD, arrhythmia, tamponade, PE, PHT
- AIRWAYS: asthma, COPD, mucus plugging, angioedema, anaphylaxis, FOB, vocal cord dysfxn
- ALVEOLI: edema, PNA, hemorrhage
- PLEURAL: large effusion, PTX
- CNS: CVA, intox (CO, ASA, BZD), met. acidosis (sepsis, DKA, etc), psych/anxiety
- OTHER: anemia, ↑abd girth, ALS/GBS/MG,

Rapid Response x6-3333 for Senior On, nursing supervisor, RT, pharmacy
DECISION TO INTUBATE:
RICU: x6-3333, ask for **"STAT RICU"**
RICU Communication Guide: have following information ready prior to intubation
- Code status & urgency/acuity of decline
- Hemodynamics: LV, RV, valves, volume status, access
- Aspiration risk: NPO, last meal, risk factors
- Difficult airway (from prior intubation notes)
- Allergies
Have ready: sedation (propofol, fentanyl, midaz), pressor (Neo >> Levo), IVF w/ push line; RICU brings paralytic
MICU/CCU: Resource RN will call for RICU; make sure attending/OI, fellow, RT, RN aware

INTUBATION IS NOT AN ACT OF WEAKNESS Do not delay intubation in patients with impending respiratory failure

Treatment

- **Supplemental oxygen therapy** (see *Oxygen Delivery Therapies* for more detail):
  - o NC: for every liter increase in O2, approx. ↑FiO_2 0.03/L (max: 6L = 0.40 FiO2, dependent on V_e/entrainment)
  - o NRB: can give FiO_2 ~0.90, but in tachypneic patient, FiO_2 ~0.60 *(due to entrainment of room air)*
  - o HFNC: FiO_2 0.6 to 1.0 at 10-60 L/min (humidified air); ↓90d mortality vs NIPPV for pts with hypoxemic respiratory failure not due to cardiogenic pulmonary edema or obstructive lung disease (NEJM 2015;372:2185)
- **NIPPV** (BiPAP for COPD; CPAP for CHF): RR >25-30, accessory muscle use, pH <7.35, P_aCO_2 >45mmHg
- **Intubation**: see **red flags** above

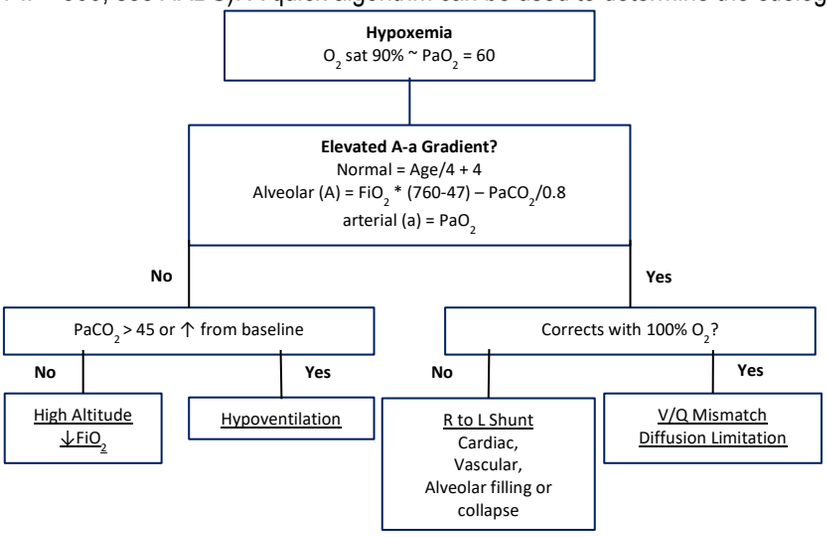
Disease Specific Treatment

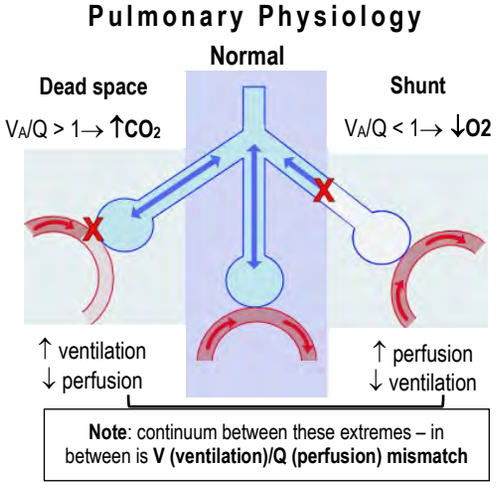
- **CHF**: CPAP, IV diuresis, nitrates (*paste or drip*, if BP room)
- **Asthma**: nebulizers (albuterol 2.5-5mg q20min or stacked DuoNeb), steroids (IV methylpred 125mg q6h), Mg (2g/20 min). Trial BiPAP ; however, if RR remains >25, VBG w/ nl or rising CO2, AMS, or bradycardia, discuss intubation. Decreasing wheeze can portend respiratory collapse (sign of worsening air movement/increased bronchoconstriction)
- **COPD**: BiPAP, stacked DuoNebs, steroids (IV methylpred 60-125mg); abx if 2/3: ↑sputum volume, purulence, dyspnea
- **Hemoptysis (massive)**: place pt in lateral decub, bleeding lung side down; volume resuscitate, reverse coagulopathies, call IP
- **Mucus plugging**: airway suctioning, percussion/chest PT, guaifenesin, place pt in lateral decubitus, good lung side down
- **PE** (see *VTE Treatment);* if high suspicion and no contraindication, start **empiric AC** (LMWH therapeutic faster vs UFH gtt). **Consult PERT x4-7378**
- **PTX**: if unstable, bedside needle thoracostomy (**STAT page Thoracic Surgery**, *14G angiocath, 5th ICS at mid-axillary line or 2nd ICS at mid-clavicular line*); then chest tube (Thoracic Surgery or IP)
- **Pleural effusion**: thoracentesis (see *Thoracentesis*; must be performed by IP or supervised by pulm attending)
- **Opioid overdose**: Narcan 0.4-2mg IV/IM q2min, observe response, uptitrate to adequate RR. Given short half-life, consider gtt if responsive to bolus at 2/3 of bolus dose per hour (ex: 0.2–0.6 mg/h)
- **Anaphylaxis**: MGH Pathway Initial: epi *(1:1000)* 0.3mL = 0.3mg IM, q5-15min PRN. Other agents may follow: diphenhydramine 25-50mg IV, nebulized albuterol, methylprednisolone 1-2mg/kg IV, If persistent may require epi gtt.
- **ACS** (*see ACS)*: ASA 325mg, atorvastatin 80mg, nitrates (SL/nitropaste→ gtt), heparin, consult Cardiology

Cassandra Fiorino

Pulmonary & Critical Care — Hypoxemia & Hypercapnia

Respiratory Failure: inability to oxygenate (deliver O_2) or ventilate (blow off CO_2). Can be **hypoxemic** (PaO_2 <60mmHg), **hypercapnic** ($PaCO_2$ >45mmHg), or both. **P:F Ratio** ($P=PaO_2/F=FiO_2$) quick surrogate for A-a gradient (consider ARDS if P:F <300; see *ARDS*). A quick algorithm can be used to determine the etiology of hypoxemia based upon ABG results.

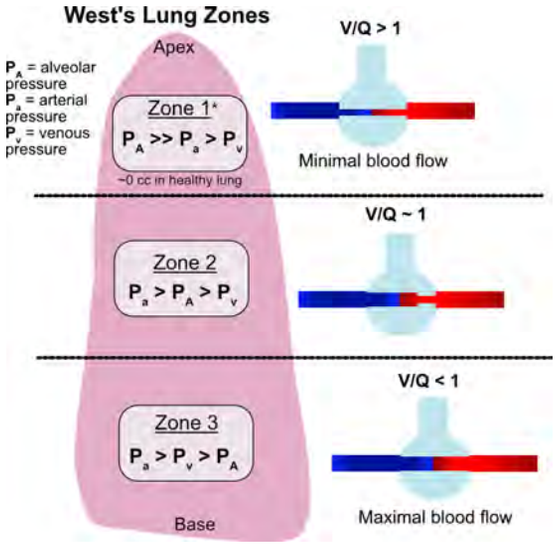




**Pulse oximetry may be inaccurate in dark skin tones, delaying detection of hypoxemia. Consider ABG (JAMA 2022;182(7))

Hypoxemic Respiratory Failure

- **Hypoventilation & low FiO_2**: decreased O_2 delivery to lungs
- **V/Q mismatch**: imbalance in delivery of oxygenated air & blood flow; *note: ↑pulmonary vasoconstriction can ↓hypoxemia by ↓Q to poorly ventilated regions, ↑V/Q matching (ratio closer to 1)*
  1. *FOCAL* alveolar infiltrates: **pus (PNA)**, **edema**, **hemorrhage (DAH), cells (cancer), aspiration**
  2. Airway: **asthma**, **COPD**, **bronchiectasis**
  3. Vascular: **pHTN**, **PE**
- **Shunt**: flow of blood through lung without encountering oxygenated air, *"perfusion without ventilation"* (severe V/Q mismatch). Will not improve with supplemental oxygen *(refractory hypoxemia)*
  1. *DIFFUSE* alveolar infiltrates: **above + ARDS**
  2. Alveolar collapse: **PTX, atelectasis, mucus plug**
  3. Intra-cardiac/pulm shunts: **PFO/ASD/VSD** *(↑PEEP worsens this by ↑ west zones 1&2 = ↑RV afterload)*, **AVM** (e.g., hepatopulm.)
- **Impaired diffusion (↓DLCO)**: hypoxemia worse w/ exertion
  ILD (correlates with severity on CT), pHTN, advanced COPD



(JAP 1964;19:713)

Hypercapnic Respiratory Failure

- **"Won't breathe" (↓RR)**: **sedatives**, **obesity hypoventilation**, brainstem stroke/tumor/infection, central sleep apnea, compensation for metabolic alkalosis (chemoreceptors), hypothyroidism (myxedema coma)
- **"Can't breathe" (↓V_A)**:
  1. ↑Dead space (airspace not participating in gas exchange; *"V without Q"*)
     - Dead space = **anatomic** (~150cc upper airway air without perfusion) + **alveolar** *AKA West Zone 1* (~0 normally; in disease, capillaries get destroyed or compressed →↑V_D)
     - Parenchyma: **emphysema**, **ILD**/fibrosis, **HF, PNA, ARDS**
     - Airway: **asthma/COPD**, CF, bronchiectasis, OSA, tumor, **high PEEP**
     - Vascular: **severe PE** -> wasted V due to blocked Q; most apparent if unable to augment ventilation eg in ALS (more often see ↓pCO2 secondary to hyperventilation)
  2. Chest wall/pleural constraints →↓lung volume: effusion/fibrosis, obesity, kyphosis/scoliosis, abd distension, PTX
  3. Neuromuscular (Neurol Clin 2012;30:161): trend at bedside with single breath test (non-intubated pts), negative inspiratory force (NIF) (intubated pts). **Consider EMG**. Ddx: **neuropathy** (C-spine/phrenic nerve, GBS, ALS, polio), NMJ disorder (MG, botulism), myopathy (polymyositis/dermatomyositis, hypophosphatemia), critical illness
- **↑CO_2 production (V_{CO2})**: **↑WOB, fever**, seizure, sepsis, steroids, overfeeding, thyrotoxicosis

Acid-Base Interpretation

Hypercapnia→ Resp acidosis (↑pCO2)
- Acute: HCO3 ↑ by 1 (per pCO2 ↑ 10)
- Chronic: HCO3 ↑ by 3-4 (per pCO2 ↑ 10)

Hypocapnia→ Resp alkalosis (↓pCO2)
- Acute: HCO3 ↓ by 2 (per pCO2 ↓ 10)
- Chronic: HCO3 ↓ by 5 (per pCO2 ↓ 10)

Pulmonary & Critical Care — Non-Invasive Oxygenation/Ventilation

Conventional Oxygen Delivery Devices

Recommendations for Supplemental Oxygen Therapy

- Target SpO_2 91-96%: Recent trials of O_2 targets found no benefit to higher/lower targets in critical illness (ARJCCM 2021, PILOT)
- Lower target (SpO_2 88-92%): At risk for hypercapnic respiratory failure (COPD, OHS, OSA, decreased central respiratory drive, neuromuscular respiratory disease)
- Higher Target (~SpO_2 ~100%): CO poisoning, cluster headaches, sickle cell crisis, pneumothorax

Mask Type	Flow (LPM)	FiO_2 (%)	Notes	Aerosol?
Nasal Cannula	1 - 6	24 - 40	FiO_2 ↑by 0.04 per L Allows patient to eat/speak. Consider humidification if >4LPM	N
Oxymizer	1 - 15	24 - 45	20mL reservoir allows for higher FiO_2 compared to NC	N
Simple Facemask	6 - 10	30 - 60	Flow rates < 6LPM lead to re-breathing of CO_2	N
Face Tent (Shovel mask)	5 - 10	24 - 50	Less claustrophobic, FiO_2 variable (lots of leakage). Use if stable O_2 needs Offers humidification without a mask	Y, if humidified
Non-Rebreather	10 - 15	60 - 100	**Consider first for acute hypoxemia (easily accessible)** ↑FiO_2 with tachypnea and ↑Vt due to entrainment Titrate flow rate to avoid reservoir bag collapse (<1/3) on inspiration	N
Venturi	Var. color	24 - 50	Color-coded adapters determine flow and FiO_2 independent of ventilatory demand. Useful for set SpO_2 goals (e.g., COPD) **NOT** for acute respiratory distress	Y, if >15 LPM or humidified

Racial disparities in pulse oximeter measurement: ↓accuracy in Black patients w ↑occult hypoxemia (NEJM 2020, Annals of ATS 2022)

High Flow Nasal Cannula (HFNC) & Noninvasive Positive Pressure Ventilation (NIPPV)

NEJM 2022;387:1688-98

	HFNC	NIPPV (CPAP + BiPAP)
Parameters	**Flow**: 10-60 LPM (up to 80 at some institutions) **FiO_2 (%)**: 21-100 ~0.7-4.2cm H_2O of PEEP w/ mouth closed (~0.7cm H_2O/ 10LPM)	**CPAP:** constant level of pos. pressure; targets oxygenation **BLPAP (or BiPAP™):** provides positive inspiratory pressure (IPAP) above PEEP with each pt-triggered breath; targets ventilation and oxygenation
Physiologic Effects	**Oxygenation:** ↑delivery of O_2, some PEEP **Ventilation:** ↑ventilation (↓dead space during expiration) **Other:** Humidification ↑mucociliary clearance of secretions	**Oxygenation:** ↓atelectasis, ↓upper airway obstruction, ↓WOB (& O_2 consumption) **Ventilation:** ↑tidal volume and minute ventilation (via IPAP) **Other:** ↓venous return (↓LV & RV preload), ↓LV afterload
	Clinical Scenarios	
Acute COPD exacerbation w resp. acidosis	**Strong indication for BiPAP** (ERS/ATS: ERJ 2017;50) **BiPAP**: off-load respiratory muscles, counter-act dynamic hyperinflation, ↑ventilation ⇨ ↓mortality, ↓intubation, & ↓ LOS (Cochrane Rev 2017). Asthma can be treated similarly but there is less evidence to support.	
Acute cardiogenic pulmonary edema	**NIPPV (BiPAP / CPAP)** ↓intubation, ↓in-hospital mortality by ↓ WOB, ↑FRC, ↓LV / RV preload, ↓LV afterload (NEJM 2008;359:142; Cochrane Rev 2013)	
Acute hypoxemic respiratory failure (AHRF)	Mixed evidence for NON-hypercapnic resp. failure May ↓intubation, but no Δ in mortality or LOS vs standard O2 tx (Cochrane 2020). Consider 1st if ILD, ARDS physio. May be non-inf to BIPAP in PNA. Can be used as rescue in asthma or in pts that can't tolerate bipap to help w/ dead space wash out along w/ ongoing eval. for intub.	**NIPPV** may ↓mortality & ↓intubation (JAMA 2020;324:57). Consider if also significant hypercapnia eg OHS, neuromuscular failure (e.g. ALS, MG). Caveats: (AJRCCM 2017;195:67-77) • **P:F < 150**: ↑ death vs. up-front intubation • **TV > 9-9.5 cc/kg IDW:** ↑death, ↑intubation
Post-extubation	Extub. to NIPPV or HFNC ↓ reintub. and post-extub. resp. failure in ↑risk pts: COPD, obesity (JAMA 2016;316:1565)	

Contraindications to NIPPV:

- **Risk of delay**: emergent indication for intubation, acute life-threatening non-respiratory organ failure
- **Risk of aspiration (d/t gastric insufflation)**: cannot clear secretions, AMS if pt cannot remove mask (*exception*: AMS due to hypercapnia)
- **Risk of injury**: PTX (can induce tension physiology), recent esophageal anastomosis or tear, cannot tolerate ↓preload from ↓venous return, recent facial trauma/surgery

Monitoring for and Preventing Failure

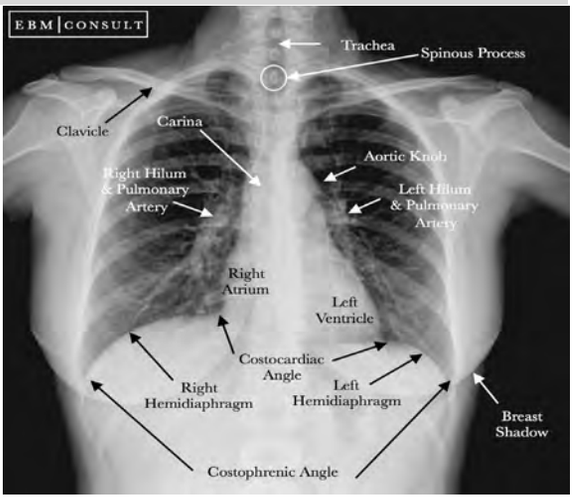
- Risk of failure varies based on cause (15-20% aeCOPD vs 40-60% AHRF) and ↑with severity of respiratory failure
- ROX index: tool for prediction of HFNC failure & monitoring for need for intubation in pts with pneumonia (AJRCCM 2019;199:1468-76)
- **HACOR score**: tool for prediction of NIPPV failure & need for intubation (ICU Med 2017;43:192-9)
- **Sedation**: IV precedex, haldol, and zyprexa can be considered to help pts tolerate NIPPV w/o suppressing resp drive (see *Sedation)*

BiPAP/HFNC on the floor: huddle with nursing and RT (also notify Sr On). Trial BiPAP or HFNC for 2-3 hours and assess response; consider ABG/VBG to assess oxygenation/ventilation. If no improvement, discuss escalation of care to ICU
REMEMBER: BiPAP/HFNC MUST NOT DELAY AN INDICATED INTUBATION!

Pulmonary & Critical Care — Interpretation of Chest Imaging

CHEST X-RAY

Systematic approach to CXR (ABCDEF approach):



1. **(A)**ssess technical quality and **(A)**irways:

- Rotation: ensure spinous process bisect btwn medial end of clavicles
- Lung volumes: adequate inspiratory effort is 9-10 posterior ribs
- Penetration: good when vertebral bodies visible behind cardiac silhouette
- Airways: look for narrowing, deviation, foreign bodies. ↑ITP pushes trachea away (PTX). ↓ITP pulls trachea towards (atelectasis/plugging).
- **Always compare previous studies.**

2. **(B)**ones/soft tissue: subcutaneous air, rib fractures, cervical ribs

3. **(C)**ardiac Silhouette (mediastinum/hilum): AP films ↑ cardiac silhouette. CT ratio=max cardiac width/max thoracic width, >50% suggests cardiomegaly (only PA films). Widened mediastinum generally >8cm (watch out for rotation).

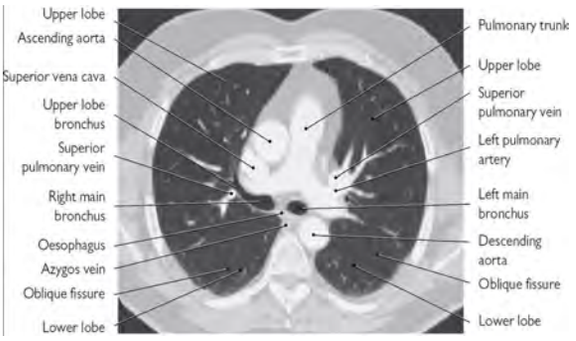
4. **(D)**iaphragm (gastric bubble): left hemidiaphragm usually lower than right. Flattening of diaphragm sensitive for emphysema.

5. **(E)**ffusions: blunting of CP angle. Small effusions seen 1st on PA lateral. Fluid not seen on upright chest until >250ml. ↓ sensitivity when semi recumbent or supine. Can assess free flowing vs. loculated effusions on lateral decubitus view (free flowing will track equality on horizontal plane vs. loculated will not).

6. **(F)**ields (lung fields) & **(F)**oreign bodies (lines/drains): Look for focal vs. diffuse processes PTX, PNA, pulm edema. Look for s*ilhouette sign* (loss of the normal visible boarder of an intrathoracic structure) that indicates pulmonary density. Look for lines/tubes (see *Interpretation of Common Studies*). ETT best 3-5cm from carina, adjust if not.

CT CHEST

- To characterize abnormal CXR w/ cross-section or w/ suspicion for pathology despite unrevealing CXR
- HRCT (thin-section CT, <2mm): for diagnosing diffuse lung path. Must be non-con. Includes expiratory, inspiratory, prone and supine images.

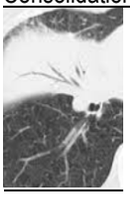


Approach to interpretation:

- Review scout imaging: gives anatomic overview.
- Review lines/tubes, extra-thoracic abnormalities.
- Mediastinum/Heart/Vessels: soft tissue window: LV>RV normally. Diameter of main PA should be < ascending aorta (PAd >/= 29 mm: PPV 97% for pHTN, Pulm HTN radiology). Cor calcium visible on non-con.
- Airways: review in soft tissue and lung windows. *Inspiratory HRCT*= round trachea**;** *Expiratory HRCT*= "D-shaped" trachea.

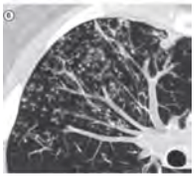
Common Findings	Definition	Associated Etiologies
Consolidations	Complete filling of alveoli, dense ↑ attenuation obscuring underlying lung architecture +/- air bronchograms	PNA > Malignancy
GGO's	Partial filling of alveoli +/- interstitium, appears as hazy ↑ lung attenuation (light gray) that does NOT obscure underlying architecture	Infxn, edema, blood, fibrosis, malig
Tree-in-Bud (AJR 2009;193:472)	Branching linear opacities & nodules that represent dz'd lobular bronchioles or bronchiolitis & filling with fluid, pus, mucus, or pulmonary tumoral emboli	Infxn (incl. tb), CTD, ABPA, carc. Endarteritis, CF
Emphysema	Airspace enlargement > 1-2 cm in diameter. "Bleb"= similar, but < 1-2 cm	COPD, congenital, spont
Mosaic Attenuation	Patchy low and high atten. areas due to air trapping, decreased perfusion, GGOs. Air trapping identified as worsening with expiratory films.	HP, OLD, CTEPH, Infxn, Edema/hemorrhage
Honeycombing	Clustering of cystic airspace disease. Microcystic <4mm, macrocystic >4mm	ILD: NSIP <4mm; IPF>4mm
Subpleural Retic	Linear opacification of the inter/intralobar septae around 1 cm from pleura.	UIP>NSIP, NL w/ aging
Atelectasis, Effusion	Atelectasis enhances w/ con, resolves proned. Effusion more homogenous	

Consolidations



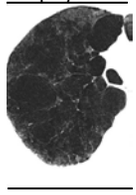
GGOs

Tree-in-bud opacities



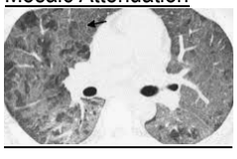
Centrilobular Nodules

Emphysema



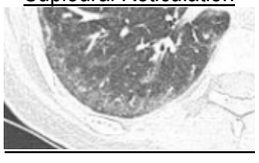
Atelectasis & Eff.

Mosaic Attenuation

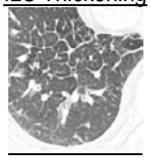


Honeycombing

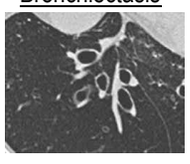
Supleural Reticulation



ILS Thickening



Bronchiectasis



PULMONARY FUNCTION TESTING (PFTS)

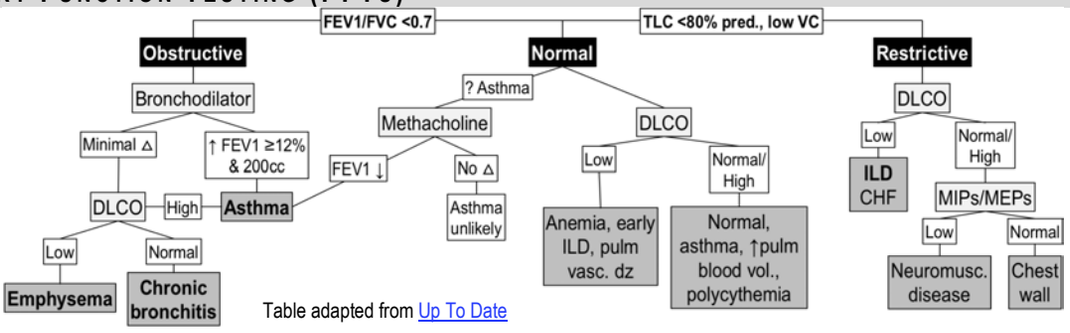


Table adapted from Up To Date

ASTHMA (GINA 2023, NAEPP 2020)

Definition: heterogeneous condition with resp sx (wheeze, SOB, chest tightness, cough) and variable expiratory airflow limitation

Symptoms	Resp sx (wheeze, SOB, cough, chest tightness) that vary over time & intensity, worse @ night/early AM
Triggers	Exercise, cold air, allergens, irritants (smoke, perfume), viral respiratory infections, drugs (ASA, NSAIDS, β-blockers)
Spirometry	Obstructive (FEV1/FVC < LLN or 0.7), reverses w/ bronchodilator (↑0.12 or >200mL), worsens w/ methacholine (can be nl before provocation, FEV1 ↓ 0.2)
Endotypes	T2-high (atopic triad, ↑Th-2/eosinophil response; steroid-sensitive), T2-low (poorly understood, often steroid-refractory)
New-onset adult cases ddx: systemic disease (ABPA, EGPA, systemic mastocytosis), occupational asthma (10-25%; NEJM 2014;370:640), ASA-exacerbated resp. disease (7%, esp. if nasal polyps; J Allergy Clin Immunol 2015;135:676)	

OUTPATIENT CARE

- **Controller + reliever**: stepwise based on severity (*below*); step up if not controlled; step down if well controlled 2-3mo
  - Note: *GINA guidelines rec ICS-containing controller*; no longer rec. tx w/ SABA a/w ↑allergic responses & airway inflammation, ↓response, & overuse a/w ↑severe exacerbations, though NAEPP still recs SABA PRN
  - May be some phenotypes w/ low eos. inflamm. (<2% in sputum) in whom ICS ↓effective (NEJM 2019;380:2009)
- **Non-pharm interventions**: smoking cessation, regular physical activity, vaccines, breathing exercises, weight loss if obese

NEJM 2019;238:2020; NEJM 2018;378:1865; NEJM 2018;378:1877; AJRCCM 2005;171:129; Chest 2006;129:246; Lancet 2011;377:650

Adapted from GINA 2023	**Mild intermittent STEP 1**	**Mild persistent STEP 2**	**Moderate persistent STEP 3**	**Severe persistent STEP 4**	**Severe STEP 5**
Symptom frequency	Infrequent	2-7d/week	Most days	All day	All day
Nighttime awakenings	<2/month	3-4n/month	>1/week	Nightly	Nightly
Exacerbations	0-1/year	>2/year	>2/year	>2/year	>2/year
Baseline FEV1	Normal	Normal	60-80% predicted	<60%	<60%
Controller (Preferred)	**None**	**None**	**Low dose ICS-formoterol**	**Med dose ICS-formoterol**	**Med dose ICS-formoterol and LAMA** *Consider: phenotypic assessment and biologics**
Controller alternative	*Low-dose ICS whenever using PRN SABA*	*Low dose ICS*	*Low dose ICS-LABA***	*Med/high dose ICS-LABA*	*Same as above, can consider LTRA, azithro*
Reliever (Preferred)	PRN low dose ICS-formoterol				
Reliever alternative	*PRN SABA or ICS-SABA*				

***Biologics**: anti-IL4R-alpha, anti-IgE, anti-IL5, anti-TSLP. **LABA w/o ICS ↑ rates of death (CHEST 2006;129:15; NEJM 2010;362:1169).

ASTHMA EXACERBATIONS

OUTPATIENT: short course pred. 40-50mg x5-7d + controller/reliever regimen, consider 4x controller ICS if mild (NEJM 2018;278:902)
INPATIENT: assess severity of exacerbation (VS, mental status, SpO_2, WOB, PEF < 50% severe), consider VBG/ABG, CXR
Severe: ↑resp drive→↑RR→↓pCO_2, nl/↓pH suggest resp. failure. If sig hypoxemia, consider resp. failure vs PTX, PNA, PE, plug, etc.

Floor Patient	ICU Patient (Thorax 2003;58:81)

- **Bronchodilators**: albuterol (2.5-5g) ± ipratropium (0.5-1.5mg) q20m x3
  o DuoNebs in ED a/w ↓admit (Cochrane Rev 2017)
  o SABA mono-tx unless severe/worsening (GINA 2023, NAEPP 2020)
- **Steroids**: **pred 40-60mg** total **x5-7d** (Cochrane Rev 2016)
- **O_2** >92% (93-95% in severe; >95% increases pCO_2; Thorax 2011;66:937)
	- **Bronchodilators**: albuterol + ipratropium, **Methylpred 125mg IV q6h**
	- **NIV**: BIPAP -> BIPAP w/ sedation -> HFNC
	- **Rescue therapies**: Mg IV 2g, continuous albuterol nebs (CAB). Less data: IV epi, ketamine, inhaled anesthetic, Heliox. *ECMO=last resort*
	- **Mechanical ventilation:** large ETT (8+), ↑insp flow rate (80-100L/min), ↓V_T (6-8cc/kg), ↓RR (10-14), ↓PEEP, paralysis; **Goal:** max exp. phase, minimize hyperinflation, permissive hypercapnia

- **If impending respiratory failure**: stacked DuoNebs (x3/h), methylpred IV 60-125mg q6h, Mg IV 2g/20min, transfer to ICU	

ASTHMA/COPD OVERLAP (ACO) (GINA 2023;163; AJRCCM 2017;196:375; NEJM 2015;373:1241)

- Some patients have persistent airflow limitation together with clinical features c/w both asthma & COPD
- *ICS-containing treatment is essential*; Also need LABA and/or LAMA. Can escalate to triple therapy, biologics

Pulmonary & Critical Care

COPD

DEFINITION: persistent respiratory symptoms (dyspnea, cough, sputum production, recurrent wheezing, exacerbations) d/t abnormalities of airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that lead to persistent airflow obstruction (GOLD 2024)

DIAGNOSIS AND STAGING (GOLD 2024: AJRCCM 2017;195:557)

1. **Diagnosis**: respiratory sx + fixed obstruction w/FEV1/FVC <0.7 or LLN on spirometry post-bronchodilator
2. **GOLD *Grade*** (1-4) is defined by severity of airflow limitation (FEV1 % of predicted), helps establish prognosis & guide non-medical therapy
3. **GOLD *Group*** ("ABE") is defined by exacerbations & sx (mMRC, CAT score) guides therapy
4. **Other testing**: lung volumes, DLCO (<60% a/w sx, exercise, ↓health), exercise test (6MWT), α1-antitrypsin

	mMRC 0-1 CAT<10	mMRC ≥ 2 CAT ≥ 10
≥ 2 exacerbations OR ≥1 admission	E	
0-1 exacerbations wo admission	A	B

GOLD Grade	FEV 1 (% of predicted)
1 (Mild)	≥80
2 (Moderate)	50-79
3 (Severe)	30-49
4 (Very Severe)	<30

DIFFERENTIAL

Pre-COPD: respiratory symptoms with structural lung lesions (emphysema) and/or physiological abnormalities w/o airflow obstruction
Preserved Ratio Impaired Spirometry (PRISm): respiratory sx w/ normal ratio (FEV1/FVC > 0.7) but impaired FEV1 (< 80) after bronchodilation
Chronic bronchitis: overlapping condition; chronic cough + sputum > 3 months / yr for 2+ years**. Asthma**: see *PFTs and Asthma*
Bronchiectasis: large vol of purulent sputum, a/w bacterial ifxn, bronchial dilat on CXR/HRCT**. Obliterative bronchiolitis**: lung/BM txp, HRCT: hypodense areas on exp**. Diffuse panbronchiolitis**: Asian pts, chronic sinusitis, CXR/HRCT: diffuse small centrilob nodular opac & hyperinflation

MANAGEMENT OF STABLE COPD (GOLD 2024; NEJM 2019;381:1257); Chart w/list of common inhalers: Allergy/Asthma Resp Rx 2024

Pharmacologic interventions:↓symptoms, ↓risk/severity of exacerbations, ↑health status, survival

	GOLD A	GOLD B	GOLD E
Starting tx:	Bronchodil (LABA or LAMA)	LABA+LAMA	LABA+LAMA. If eos>300 or asthma: LABA+LAMA+ICS
Rescue therapy:	Short-acting bronchodilator		
Escalate to:	Dyspnea: LAMA + LABA Exacerbation: LAMA + LABA	Dyspnea: Switch inhaler device or molecules. Nebulizers may be helpful in severe COPD. Exacerb: Eos >100: LAMA+LABA+ICS (Lancet RM 2018;6:117), consider adding biologics (i.e. dupilumab (BOREAS Trial)); Eos < 100: Roflumilast (bronchitis) (Lancet 2015;385:857) vs. Azithro (former smokers) (NEJM 2011;365:689; Lancet RM 2014;2:361; Cochrane Rev 2018)	
Notes	• Long-acting>short-acting unless occ. dyspnea • Tiotrop may slow decline in FEV1 in early COPD (NEJM 2017;377:923)	• LABA+LAMA > mono-therapy (Chest 2014;145:981; Cochrane Rev 2015)	• Include ICS if features of asthma • LAMA+LABA+ICS > LAMA+LABA to ↓exacerbations, but may ↑PNA (TRIBUTE; IMPACT; ETHOS). *Consider d/c ICS if persist. exacerb, PNA* (if eos >300, high risk ↑exacerb. w/ d/c)

Non-Rx interventions: **Smoking cessation:**↓mortality; Annals 2005;142:233**, Vax:** Flu, COVID, PCV20 (or PCV15→PPSV23), Tdap, Zoster, RSV
Lung CA screening: annual low-dose CT (age 50-80 & ≥ 20 pack-years & has smoked in last 15y) (USPSTF 2021)
Pulmonary rehab (GOLD B/E): ↑QoL, ↑exercise capacity (Cochrane Rev 2015), possibly ↓mortality (JAMA 2020;323:1813)
Home O_2: if PaO_2 ≤55 or SpO_2 ≤88% (PaO_2 ≤59 or SpO_2 ≤89 if pulmonary HTN or Hct >55% or CHF) for goal SpO2 >90%
Nocturnal NIPPV: if daytime pCO2 >53 & nocturnal SpO_2 ≤88% (despite 2L O_2) or recent exacerb. & persistent $PaCO_2$ >53 (↓risk of readmit & mortality: JAMA 2017;317:2177) **Interventional therapies:** bronchoscopic lung reduction (emphysema + hyperinflation), bullectomy, **lung txp** (indications: progessive dx despite max rx, non-surgical candidate, BODE index 5+, frequent exacerb, low FEV1 (20-25%), or rapidly ↑ BODE)

COPD EXACERBATION (AECOPD) (ERS/ATS: ERJ 2017;49, GOLD 2024)

- **Hx**: ↑**dyspnea**, ↑/Δ sputum, and/or ↑cough < 14d; ask re: URI sx, CHF sx, VTE risk fx, prior exacerbations/steroids/intubations/abx
- **W-up**: CXR, ABG/VBG ± ECG, trop, NT-proBNP. Flu, COVID, PE (PE in 25% severe exacerb w/o clear trigger: Annals 2006;144:390)

Management:

- **SpO_2 88-92%**: hyperoxia → ↓vent. via Haldane effect & hypoxic vasoconst., ↑V/Q mismatch; ↑mortality (BMJ 2010;341:c5462)
- **Bronchodilators**: albuterol, ipratropium, DuoNebs (combo)
  - "Stacked" DuoNebs (x3 in 1h) initially → space to standing DuoNebs q4 w/ albuterol PRN q2 → space further as able
- **Steroids**: pred 40mg x5d. PO ~ IV (Chest 2007;132:1741) & 5d ~ 14d (REDUCE JAMA 2013;309:2223; Cochrane Rev 2018); some may need higher dose/longer course if severe, but ↑PNA risk
  - If severe: IV methylpred 60-125mg q6-q12x72h, budesonide neb.
- **NIPPV**: if resp acidosis (pH < 7.35 & PaCO2 > 45), severe dyspnea, ↑WOB, pers hypoxemia. ↓mortality, intub., LOS (Cochrane Rev 2004).
- **Intubation:** NIV failure, s/p arrest, aspiration/vomiting, HDUS
- **Antibiotics**: controversial; ↓mortality but challenging to identify who will benefit (Chest 2008;133:756; Coch Rev 2012)
  - Indicated if: ↑all 3 cardinal sx, 2/3 w/↑sputum **purulence**, or require NIPPV/mechanical ventilation
    - CRP may be useful (NEJM 2019;381:111). PCT may be useful but ↑mortality when used in ICU (Eur Resp Rev 2017;26; ICM 2018;44:428)
  - Choice: based on PsA risk, prior SCx, resist. ⊖ PsA RFs: FQ, CTX; amox/clav, azithro, doxy. ⊕ PsA RFs: FQ, cefe, pip/tazo Duration: 5-7d inpt; 3-5 outpt (vary by drug)
    - Concurrent CAP: treat by CAP guidelines
- **Antivirals**: oseltamivir if influenza⊕, even if ≥48-72h
- **VTE ppx**

INHALED THERAPIES FOR ASTHMA & COPD

Class	Example Meds
Short-acting β-agonist (**SABA**)	Albuterol, levalbuterol (SE: ↑HR; levalbuterol more selective so less HR effect but $$)
Short-acting muscarinic antagonist (**SAMA**)	Ipratropium (Atrovent) (SE: urinary retention, dry mouth)
Long-acting β-agonist (**LABA**)	Salmeterol, formoterol (*NB*: in asthma, do not use without ICS)
Long-acting muscarinic antagonist (**LAMA**)	Tiotropium (Spiriva), umeclidinium (Incruse Ellipta)
Inhaled corticosteroid (**ICS**) + **LABA**	Fluticasone-salmeterol (Advair), budesonide-formoterol (Symbicort), mometasone-formoterol (Dulera), fluticasone-vilanterol (Breo Ellipta)
LAMA + LABA	Umeclidinium-vilanterol (Anoro Ellipta)
LAMA + LABA + ICS	Fluticasone-umeclidinium-vilanterol (Trelegy Ellipta)

BRONCHIECTASIS (permanent airway dilatation from recurrent infxn/inflammation) (AJRCCM 2013;188:647; NEJM 2022;387:533)

Symptoms	Chronic productive cough, recurrent bronchitis/pneumonia, wheezing, dyspnea, hemoptysis, recurrent pleurisy
Etiology	**Recurrent insult**: infection (PNA, MAC, TB, PsA, childhood infections, ABPA), inhalation, GERD/aspiration **Impaired immunity**: ↓mucus clearance (CF, 1° ciliary dyskinesia [PCD]), immunodeficiency (e.g., HIV, CVID, ↓IgG) **Obstruction**: foreign body, tumor, COPD, tracheomalacia/tracheobronchomegaly, CTD (Marfan's), radiation **Systemic disease**: RA, Sjogren's, SLE, IBD, A1AT**; Idiopathic** = ~50%
Workup	**Dx:** 1) productive cough most days/week, 2) exacerbations, **and** 3) CT w/ ≥1 of: bronchial diameter > adj artery (signet-ring sign)**,** thickened bronchi w/ lack of tapering (tram track sign), radiographically visible airways in perimeter **Initial**: MDCT or DLDCT, PFTs, CBC/diff, Ig levels, sputum Cx (bacterial, mycobacterial, fungal) **As indicated**: CF eval (gene/sweat Cl^- testing), Aspergillus IgE, ANA, RF/CCP, SSA/SSB, A1AT, HIV, Ig levels; consider nasal NO (PCD), pneumococcal vaccine titers (often low), bronch w/BAL, colo (IBD), pH/motility testing
Natural Hx	Exacerbations, ↓ in FEV_1, PsA colonization → worsening disease; prog. w/ Bronchiectasis Severity Index or FACED

Chronic Management

CF: AJRCCM 2013;187:680, AJRCCM 2009;180:802; non-CF: AJRCCM 2013;188:647, ERS: Eur Resp J 2017;50, BTS: Thorax 2019:74

- **Airway clearance**: nebs (albuterol, 3% NaCl), chest PT (acapella, vest)
  - CF: add DNase to neb bundle; not effective in non-CF
- **Antimicrobials/anti-inflammatories**:
  - Non-CF: Long-term azithro ↓exacerb. but c/f ↑abx resistance (Lancet 2012;380:9842; JAMA 2013;309:1251; Coch Rev 2018; Lancet RM 2019;7:845). Ensure no NTM first
    - Intermittent abx (FLQ, β-lactam, tobra) in pts w/ ≥3 exacerb/y ↓exacerb but ↑abx resistance (Coch Rev 2022)
    - Trial inhaled abx if PsA colonization & ≥3 exacerb/y, consider eradication of new PsA isolate
  - CF: azithro + inhaled tobramycin (for PsA; alt: aztreonam, colistin)
- **Disease specific treatment**:
  - Non-CF: treat underlying cause if found; consider PPI/H_2 blocker
  - CF: *CFTR mut→ defective Cl^-/HCO_3^- transport on airway surface*
    - Potentiators open CFTR channel (**ivacaftor**); correctors bring it to surface (**lumacaftor, tezacaftor, elexacaftor, VX-659**)
    - Dual/triple tx→ long-term FEV1 benefits (NEJM 2015;373;220; NEJM 2017;377:2013; NEJM 2018;379:1599; NEJM 2019;381:1809)
    - **Pancreatic enzyme supplementation**, vitamins ADEK

Acute Exacerbation

- **Sx**: Δ in ≥3: change in cough/sputum, purulent sputum, worse dyspnea, fatigue, hemoptysis, clinical judgment (Eur Resp J 2017;49)
- **Obtain resp cx prior to abx, CXR**
- Micro: *PsA, S.aureus* > *H. flu, Moraxella, Burkholderia*; treat *Stenotrophomonas, Achromobacter* as pathogenic; *Aspergillus* in CF not always pathogenic
- **Abx**: use previous Cx data; **tx 10-14d**
  - No prior cx data: empiric FLQ (for PsA)
  - If prior R-PsA: IV abx; 2 agents – β-lactam & either FLQ or IV tobra (dosed qd)
    - *No great evidence for double coverage of PsA though is standard of care* in CF
  - If β-lactamase⊕ *H flu* or *Moraxella*: amox/clav, CTX, doxy, macrolide, or FQ
  - Cont home azithro ± tobra (practice varies)
- Steroids only w/ concom. asthma, COPD, ABPA
- Continue chronic treatment (airway clearance)

HEMOPTYSIS (expectoration of blood from lower respiratory tract) (Am Fam Physician 2022;105:144)

Etiology (common & life-threatening)	• **Airway**: bronchitis, bronchiectasis (incl. CF), masses (usually 1* lung CA), trauma (incl. foreign body) • **Pulmonary parenchyma**: infection (PNA, abscess, TB, aspergilloma), vasculitis (ANCA, anti-GBM, immune-complex, drug-induced; see *Vasculitis* and *Autoantibodies*), coagulopathy, endometriosis, inhalation injury, collagen defect, sarcoid, pulmonary hemosiderosis, trauma • **Pulmonary vascular**: PE, CHF (esp if on AC), mitral valve dz, bronchovascular fistula, aneurysm, AVM
Work-up	1) Consider pseudohemoptysis from other sources (GI or nasopharyngeal) 2) **CXR (most important),** CBC, coags, U/A (vasculitis, anti-GBM), sputum Cx, CTA chest (if stable), bronch 3) Consider NT-proBNP, D-dimer, ESR/CRP, C3/C4, ANA, ANCA, anti-GBM, APLAS, IGRA/AFB, RVP

Non-massive: if minimal (<30mL) & benign (eg. infxn/bronchiectasis): observe. If active, recurrent, >1w: CT → bronch
MASSIVE HEMOPTYSIS (>500mL/d or >100mL/h) = **life-threatening emergency** with mortality 50-80%. Asphyxiation, NOT exsanguination, is mechanism of death (maximum pulmonary blood volume ~500mL, CCM 2000;28:1684)

- **LIE PATIENT WITH SIDE OF SUSPECTED BLEED DOWN** (preserve gas exchange in unaffected lung)
- Ensure hemodynamic stability, active T&S, correct coagulopathy. Inhaled TXA may be beneficial (Chest 2018;154:1379)
- **STAT RICU** (x6-3333) → control airway if dyspneic, rapid bleed, largest possible ETT (8mm+), suction as blood can fill ETT
- **Call IP** → bronch to localize; temporize w/ balloon tamponade, bronchial blockade, electrocautery, topical vasoconstriction
  Call IR → if stable, can CTA to localize; otherwise, bronchial angiography to embolize site. *If refractory*, call thoracic surgery
- Can consider pulse dose methylprednisolone if vasculitis suspected

DIFFUSE ALVEOLAR HEMORRHAGE (disruption of alveolar-capillary basement membrane) (Chest 2010;137:1164)

Presentation: hemoptysis (can be absent in 1/3), cough, fever, dyspnea, diffuse radiographic opacities, abnl gas exchange
Etiology: capillaritis (rheum, drugs, idiopathic), bland hemorrhage (AC, ↓plt, HF), diffuse alveolar damage (ARDS, infxn, PE, drugs)
Workup: CXR, CT (diffuse GGO central > peripheral), BAL (progressively more hemorrhagic serially), labs guided by clinical picture
Management: Primarily supportive. Manage hypoxemia and treat underlying etiology, eg.:
Capillaritis/AI syndromes: Systemic glucocorticoids (pulse dose IV methylpred 500-1000mg/d up to 5 doses w/ taper), cyclophos, ritux ± plasmapheresis. Excess AC/bleeding disorder: reverse AC. (Int J Mol Sci. 2021;22:793)

Pulmonary & Critical Care — Interstitial Lung Disease

OVERVIEW

Heterogeneous group of lung diseases involving the replacement of normal lung parenchyma with varying degrees of inflammation and fibrosis (scarring), can involve any part of the lung parenchyma

Presentation: progressive dyspnea, non-prod. cough, hypoxemia (esp. w/exercise); some w/ constitutional sx (AIP, HSP, COP)

History: tempo, hx CTD/IBD/malig/thoracic XRT, rheum dz, meds, exposures (chemicals, dust, humidity, pets, barns), smoking, FHx

Exam: "velcro-like" crackles, inspiratory squeaks, clubbing, e/o CTD (heliotrope rash, Gottron's papules, mechanic's hands, synovitis, foot/wrist drop, sclerodactyly, sicca), vasculitic rash, extrapulmonary manifestations of systemic dz (sarcoid, amyloid, IBD, cancer)

ETIOLOGIES: known & idiopathic causes (ATS/ERS: AJRCCM 2013;188:733)

Idiopathic Interstitial PNAs (IIPs)	Connective Tissue Disease[7]	Exposure-Related	Granulomatous
Idiopathic Pulmonary Fibrosis (IPF)[1] Idiopathic Non-Specific Interstitial PNA **(NSIP)**[2] Acute Interstitial PNA **(AIP)**[3] Cryptogenic Organizing PNA **(COP)**[4] Respiratory Bronchiolitis-ILD **(RB-ILD)**[5] Desquamative Interstitial PNA (**DIP**)[6]	Scleroderma Sjogren's syndrome MCTD Polymyositis/Dermatomyositis Anti-synthetase syndrome Rheumatoid arthritis Lupus	**Organic**: grain, mold, birds, hay *(cause HSP)*[8] **Inorganic**: silica, asbestos, coal, metals (*causes pneumoconiosis*) **Drugs:** nitrofurantoin, MTX, amiodarone, pembro/nivo (see: PneumoTox), radiation	Sarcoidosis[9] Hypersensitivity pneumonitis[8] Mycobacterial disease Fungal disease Langerhans cell histiocytosis[10]

Radiographic Associations: (91% sensitive, 71% specific JAMA 2024)

[1] *Usual interstitial pneumonia* (**UIP**) pattern: heterogenous subpleural/basal predominant, honeycombing, traction bronchiectasis

[2] *Non-specific interstitial pneumonia* **(NISP**) pattern: lower lobe predominant, reticulation/GGOs predominantly in periphery, micronodules

[3] *Diffuse alveolar damage* (DAD) pattern: diffuse, bilateral, central>peripheral ground glass or consolidative opacities

[4] *Organizing PNA* (OP) *pattern:* bilateral peripheral, perilobular consolidations with subpleural sparing

[5] *Respiratory-bronchiolitis* (RB) pattern: centrilobular nodules (usually in upper zones), GGOs, interlobular septal thickening

[6] *Desquamative interstitial pneumonia* pattern: homogenous or patchy GGOs in mid/lower lung zones

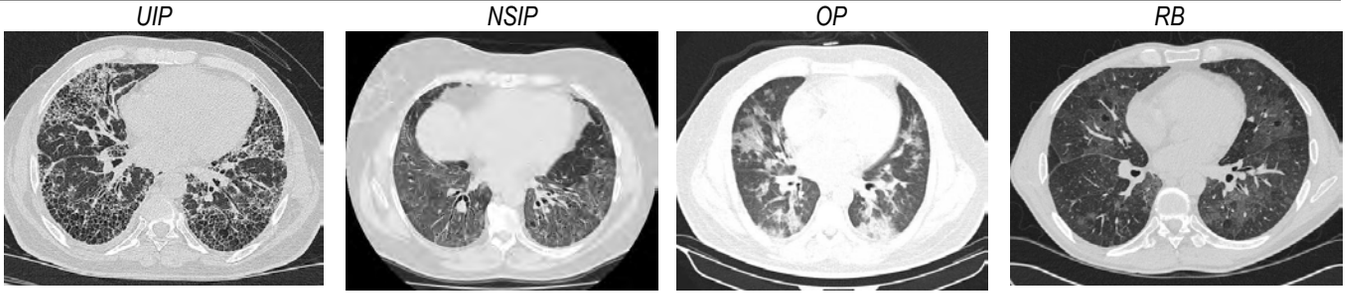
[7] May be associated with **any** pattern (UIP, NISP, etc)

[8] May be associated with RB pattern (see [5]), with progression to traction bronchiectiectasis, honeycombing, centrilobular nodules

[9] Peribronchovascular, hilar, subpleural nodules (granulomas)

[10] Stellate nodules, thick walled cysts, bullae

UIP *NSIP* *OP* *RB*



DIAGNOSTIC EVALUATION: REQUIRES A MULTIDISCPLINARY DISCUSSION

- **Exclude** fungal/atypical bact. infxn, esp. in immunocompromised pts; consider sputum bacterial/fungal culture, HIV/hepatitis testing
- **General Approach**: **remove potential environmental causes**. If improves no further w/u. If not **assess for systemic dz**. If unlikely systemic dz, HRCT (see Radiographic Associations above), consider bronch and/or biopsy based on findings
- **Labs**: CBC/diff, CMP, UA, CK/aldolase, C3/C4, autoantibodies (ANA, RF/CCP, RNP, Ro/La, Scl-70, ANCA, hypersensitivity panel, myositis panel, anti-GBM Ab)
- **Lung biopsy:** If dx unclear (atypical presentation or c/f malignancy) + Δ tx. Bronchoscopic transbronchial cryobiopsy less invasive than VATS. Not helpful if known CTD. If definite UIP, rec against (high morbidity, ↑exacerbations) (AJRCCM 2018;198:e44).
- **Assess Severity:** 6 minute walk test and PFTs: Restrictive (↓TLC, ↓FRC, ↓RV; FEV1/FVC normal to ↑); ↓DLCO can be early sign

TREATMENT

- **IPF**: (AJRCCM 2015;192:e3)
  - Acute exacerbations: ddx includes infxn, PE, HF; send BNP, trop, procal, d-dimer, blood cultures, *S. pneumo* & *Legionella* urinary antigens, extended RVP. Treat with **pred** ~1mg/kg/d & broad-spectrum **abx** (vanc/cefe/azithro) X 7d.
  - Chronic therapy: consider **pirfenidone** (antifibrotic; SE: nausea, fatigue; NEJM 2014;370:2083), or **nintedanib** (TKi; SE: diarrhea; NEJM 2014;370:2071). Promising data for new PDE4 inhibitors (NEJM 2022; 386:2178). All ↓FVC decline, may not Δ overall survival. Consider lung transplant eval. AZA, pred, NAC tx ↑mortality (NEJM 2012;366:1968). GERD tx to benefit lung disease *not* recommended (ATS 2022;205:18)
- **NSIP**: remove inciting exposures, tx underlying condition; can be **steroid-responsive** (pred 0.5-1mg/kg/d or pulse methylpred if requiring hospitalization); **2nd agent** (AZA, MMF, ritux, CYC) pending response. **Nintedanib** may benefit non-IPF progressive fibrotic disease irrespective of underlying ILD diagnosis (NEJM 2019;381:1718; Lancet RM 2020;8:453)
- **COP**: monitor; if sx persist/progress **pred** ~0.75-1mg/kg/d (pulse if fulminant)
- **AIP**: idiopathic ARDS; usually not steroid-responsive, but often trial steroids & abx as in-hospital mortality is >50%
- **Systemic Sclerosis:** permutations of Nintedanib, MMF, CYC, Rituximab, and Tocilizumab depending on symptoms (JAMA 2024)

Transplant Referral (JHLT 2022;40:1349): Any ILD: FVC<8% or DLCO<40% predicted; change in FVC ≥10%, DLCO≥15%, or FVC≥5% over 2 years w/worsening dyspnea or radiographic progression; supplemental O2 at rest or exertion. OR: IPF: Time of dx. Inflam ILD: progression of dz despite tx. CTD or familial: early referral.

Christina Shincovich

Pulmonary & Critical Care

VTE Diagnostics

CLINICAL MANIFESTATIONS

Signs/Symptoms

Deep Vein Thrombosis (DVT)

- S/Sx: pain, warmth, erythema or cyanosis, edema (esp. asymm.), palpable cord, venous distention, Homan's sign (sudden dorsiflexion of ankle w/ knee flexed to 30˚ → pain in upper calf); **none Sn/Sp** (JAMA 1998;279:1094); **can be asx**
- Types: ***proximal*** = iliac, femoral, popliteal veins; ***distal*** = calf veins below knee (ant./post. tibial, peroneal, soleal, gastrocnemius)
  - Massive iliofemoral DVT: *phlegmasia alba dolens* (edema, pain) → *phlegmasia cerulea dolens* (cyanosis, venous gangrene)
  - May-Thurner syndrome: anatomic variant → compression of L common iliac vein by R iliac artery → LLE DVT and/or swelling
- Central venous catheters are most common cause of upper extremity DVT (PICC > CIC > Ports) (Hematology ASH 2014;1;306).
- Ddx: superficial thrombophlebitis, cellulitis, arthritis, arterial occlusion, varicose veins, lymphedema, ruptured Baker cyst, chronic venous insufficiency (Arch IM 1998;158:2315)

Pulmonary Embolism (PE) (EHJ 2020;41:543)

- Sx: **dyspnea**, **pleuritic CP**, **cough**, orthopnea, leg swelling/pain, syncope, hemoptysis, diaphoresis, palpitations, **can be asx**
- (NEJM 2016;375:1524; JACC 2019;76:744)
- Signs: **tachypnea**, **tachycardia**, hypoxemia, hypotension, rales, S4, ↑P2, ↓breath sounds, JVD, fever, wheezing, RV heave, pleural friction rub, S3
- EKG Δs: sinus tach., atrial arrhythmias (AF, AFL), RAD, RBBB, inf. Q, anterior STΔs/TWIs, S1Q3T3 (ERJ 2005;25:843)

Risk Factors: Virchow's triad of venous stasis, vascular injury, hypercoagulability (Circulation 2003;107:I9; ERJ; 2020;41;543)
Risk factors tend to be additive

Strong	Moderate		Weak	
- Hospitalization for HF or AF (w/in 3 mo) - MI (w/in 3mo) - Hip/knee replacement - Lower limb fracture - Major gen. surgery - Major trauma - Spinal cord injury	- Thrombophilia - Prior VTE - Arthroscopic knee surgery - CVC (Lancet 2013;382:311) - Estrogen-containing meds - Pregnancy (postpartum) - IVF - Malignancy - Some forms of chemotherapy	- CHF (JACC 2020;75:148) - Resp. failure, asthma (ERJ 2014;43:801) - Paralytic stroke - IBD, nephrotic syndrome - Infection/sepsis (Chest 2015;148:1224) - Autoimmune disease, IBD - ESAs	- Bed rest >3d - Immobility due to sitting (e.g. airplane, car) - Increased age - Lap surgery (e.g. CCY) - Obesity (Circ 2008;117:93) - Pregnancy (antepartum)	-CKD (J Thromb. Haemost 2014;12:1449) -Diabetes - Cirrhosis (Thromb Haemost 2017;117:139) - Varicose Veins

DIAGNOSIS/RISK STRATIFICATION (ASH: Blood Adv 2018;2:3226; AHA: Circ 2011;123:1788; ESC: EHJ 2019;41:543; JAMA 2018;320:1583)

- **Pre-test prob**: Wells for LE DVT and PE, Constans' for UE (Thromb Haemost 2008;99:202), Geneva for PE
  - If **low** (or mod. DVT), can r/o w/ D-dimer (see below) or PERC score for PE; if D-dimer ⊕ need further eval. If **high** (or mod. PE) → imaging
  - Wells score discriminates risk of VTE in outpatient settings; not sufficient to rule out DVT in hospitalized patients (JAMA 2015; 175; 1112)
- **DVT diagnosis**: venous Doppler US of lower or upper extremity (LENI, UENI).
- **PE diagnosis**:
  - CTPA: study of choice; may also detect alternate dx (NEJM 2006;354:2317)
  - V/Q scan: validated (JAMA 1990;263:2753). Performed if c/i to CTPE, **Need nl CXR** (minimize other causes of V/Q mismatch), cannot be done urgently
  - LENIs: if suspect PE, unable to CT or V/Q, & ⊕, can treat; if ⊖, however, does not exclude PE (clot may have migrated or be from another source)
  - Echo: most useful for risk stratification (not dx), though demonstration of clot or new RV strain can provide presumptive diagnosis if needed rapidly
  - ABG: can see hypoxemia (↑A-a gradient, normal in ~20%), resp. alkalosis

INTERPRETING D-DIMER (nl <500)

- If nl and low pretest prob, **excludes DVT/PE** (NEJM 2003;349:1227; JAMA 2006;295:199; Thromb Haemost 2009; 101:886)
- **Adjusted D-dimer**: → ↓imaging w/o ↑ in PE
  - *Age-adjusted*: if >50, use age x10 as cut off (JAMA 2014;311:1117)
  - *Prob.-adjusted*: use of <1000 cutoff w/ low prob. (NEJM 2019;381:2125)
- Ddx for ↑D-dimer: arterial thrombus (MI, stroke, AF/intracardiac, acute limb ischemia), DIC, CA, inflammation/infection, ESLD, CHF, renal disease, ↑age, aortic dissection, trauma, surgery

- **PE risk scores: PESI** (PE Severity Index): **prediction of morbidity/mortality in patients w/ newly diagnosed PE,** sPESI (simplified PE Severity Index), and BOVA for PE complications in HDS patients.

Risk	Risk Stratification			
	HDUS: shock, SBP <90, cardiac arrest	Elevated Cardiac Biomarkers[a]	Imaging Evidence of RV Dysfunction[b]	PESI Class III-V and/or sPESI≥1
High*	+	+	+	+[c]
Intermediate-High	-	+	+	+
Intermediate-Low	-	One of two +		+
Low	-	-	-	-
*Syncope and Clot in Transit are also considered High Risk				

[a] Biomarker Evidence: ↑hs-TnT: ≥14 in age <75 & ≥45 in age >75 may ↑NPV (ERJ 2015;45:1323); ↑NT-proBNP (ERJ 2014;43:1669)
[b] Imaging Evidence: CT: RV/LV diameter ratio >0.9 (EHJ 2011;32:1657); TTE: RV Overload/Dysfunction - enlarged RV, flattened IVS, mod/severe TR, McConnell's Sign (RV free wall akinesis sparing apex; Circ 2008;118:517), ↓TAPSE (JEM 2020;58:449).
[c] Hemodynamic instability and confirmed PE on CTPA and/or RV dysfunction on TTE = high-risk. PESI classes/cardiac biomarkers unnecessary.

Pulmonary & Critical Care

VTE Management

MANAGEMENT OF VTE (CHEST: Chest 2021;160:545); ESC: EHJ 2020;41:543); ASH: Blood Adv 2020;19;4693)

Proximal DVT (popliteal, femoral, iliac vv.)

Anti-coagulate (unless contraindications), regardless of sx

Agent: **DOAC** > VKA > LMWH; if malig.: **DOAC > LMWH** > VKA
(for dosing & info on choosing agent, see AC and AC Mgmt sections)
Duration: at least 3mo for all. Individualized decision to extend >3 mo, balancing bleeding risk with risk factors of recurrence (eg provoked vs non-provoked, malignancy-related or not, APLS or not)

If stop AC, consider ASA 100mg if no contraindications (NEJM 2012;367:1979; NEJM 2012;366:1959; Circ 2014;130:1062)

IVC filter: Only if contraindications to AC (e.g. active bleeding, recent/planned high bleeding-risk procedure, major trauma, acute ICH)

- **Remove** once no longer needed (typical implantation time ~1-2mo; JVIR 2011;22:1522). Complications incl. IVC thrombosis, acute/recurrent DVT or PE, filter migration/erosion/fracture

Distal DVT (calf: ant./post. tibial, peroneal vv.)

Serial imaging vs. anticoagulation
Serial imaging: if asx, low risk for extension, or high risk for bleeding

- **Repeat US** at 1-2w (1/3 will extend; ↓risk in muscular veins: soleal, gastrocnemius)

Anti-coagulate (same AC regimen as proximal DVT) if:

- Severe symptoms
- RFs for extension: ⊕ D-dimer, extensive (>5cm, mult. veins, >7mm in diam.), close to prox. veins, no reversible provoking factor, active CA, h/o VTE, inpt
- On serial imaging, extends into proximal veins. AC also suggested if extends but remains in distal vein
- Patient prefers treatment over serial imaging

Post-thrombotic syndrome: Long-term sequelae of DVT due to poor venous flow. Treatment with compression +/- endovascular/surgical intervention (Cardiovasc Diagn Ther 2016;6;623).

UE DVT (NEJM 2011;364:861): brachial, axillary, subclavian; ↓complications vs. LE DVT. Tx same as LE DVT. If PICC/CVC (catheter-associated), no need for catheter removal if needed/functional/⃠infected; poor evidence for whether to initiate AC.

Bleeding risk: low = 0 RFs (1.6%/3mo; 0.8%/y after 3mo); mod = 1 (3.2%/3mo; 1.6%/y); high = ≥2 (12.8%/3mo; ≥6.5%/y)
RFs: age >65-75, previous bleeding, CA, renal failure, liver failure, thrombocytopenia, prior CVA, DM, anemia, anti-platelet tx, poor AC control, ↓functional capacity, recent surgery, frequent falls, AUD, NSAID use

Further diagnostic testing in unprovoked VTE: age-appropriate cancer screening (found in 5% within 1y; Annals 2017;167:410), hypercoagulability w/u limited during acute episode

***Superficial vein thrombosis**: Tx w/reduced-dose DOAC for 45 days in some patients (Chest 2021;160;545), otherwise, heat/elevation*

High Risk PE

PERT c/s (x47378): for **intermediate-high or high risk, consider SHOCK c/s (p11511) for high risk**

Resuscitation:

- Cautious IVF: can trial if CVP low, but ↑RV distention →RV ischemia + septal bowing→↓LV SV →↓CO
- Inotropes: if low CO, consider dobutamine
  Vasopressors: norepi, epi, or vaso
- O_2: HFNC preferred. *Mech vent high risk*: HoTN from induction & PPV → ↓venous return → ↓RV CO, ↑RV failure
- Circulatory collapse/arrest: Pulse = tPA Pulseless = TNK and CPR for 15 minutes to ensure circulation; eval for VA ECMO
- **Anticoagulation**: LMWH vs UFH (w/ bolus)

Thrombolysis: systemic, though some cases warrant catheter-directed tPA thrombolysis
Embolectomy: if thrombolysis contraind/fails; can be catheter-directed; surgery if all options contraind/fail or if clot in transit in RA/RV, PFO

Intermediate Risk PE

Anticoagulation: LMWH preferred > UFH (faster time to therapeutic range) unless impending hemodynamic collapse, thrombolysis (or CrCl <30 or severe obesity).

Intermediate-high risk: transition to long-term AC agent after 48-72h of stability.
Intermediate-low risk: transition after 24h.

Thrombolytic therapy (catheter-directed preferred over systemic) in select pts: (Circ 2011;123:1788) No strict guidelines, indications include: developing shock, resp failure, mod/severe RV dysfunction on TTE (RV hypokinesis, RVSP >40) w/ ↑↑ hs-TnT/NT-proBNP (>900)

- Routine tPA in int. risk PE → ↓hemodynamic decomp., no clear long-term Δ in mortality; ↑major bleeding & hemorrhagic CVA (NEJM 2014;370:1402; JACC 2017;69:1536)

Low Risk PE

Anticoagulation:
See above (DVT) and AC, AC Mgmt sections

Discharge: if no other reasons for hospitalization, can d/c; can use Hestia score to stratify for outpatient treatment

Isolated Subsegmental PE (w/ no DVT): Rule out proximal DVT. If low risk of recurrent VTE, can consider surveillance with repeat imaging. If higher risk, anticoagulate (Chest 2021; 160:e545)

Thrombolysis: → ↓mortality (Am J Card 2019;123:684; JAMA 2014;311:2414; CDSR 2021;4:CD00437)
Systemic: Patient with pulse = tPA 50-100mg/2h. Cardiac arrest = weight based TNK over 5 seconds (see ellucid thrombolysis guidelines). Hold AC during infusion (but do not delay if got LMWH), restart heparin when PTT <2x ULN. Follow fibrinogen q6h.

- *Absolute contraindications*: intracranial neoplasm, CNS surgery/trauma <2-3mo, h/o ICH, active bleeding, non-ICH stroke <3mo

Catheter-directed: infused into pulmonary artery via PA catheter, significantly less lytic agent given than in systemic lysis. May be preferred if high-risk for bleeding, failed systemic thrombolysis, or otherwise selected pts; can couple w/ US-assisted thrombolysis (EKOS) to enhance mechanical breakdown of thrombus or suction thrombectomy. ↓ in RVSP, ↓RV/LV ratio, no data for mortality benefit (Circ 2014;129:479; JACC Card Interv 2015;8:1382; Am J Med 2019;132:240; Am J Card 2019;124:1470)

PERT (x47378): call if large PE w/ abnormal VS (tachycardia, hypotension), evidence of RH strain (TTE, EKG, biomarkers), saddle PE.
SHOCK (p11511): call for consideration of ECMO if worsening refractory hypoxemia or hemodynamic instability
Order: CBC/diff, BMP, LFTs, lactate, D-dimer, ABG, PT/INR, PTT, T&S, NT-proBNP, hs-TnT, EKG, CT-PE, LENIs, TTE

Monitoring: Routine evaluation at 3-6mo; in continued symptomatic patients, consider PH/CTEPH (evaluate w/ V/Q scan, TTE, BNP and/or CPT).

Pulmonary & Critical Care

Pulmonary Hypertension

Pulmonary Hypertension = mean PA pressure (mPAP) ≥20 mmHg
PVR = (mPAP - PCWP) / CO; rearranged: mPAP = (PVR x CO) + PCWP
∴ ↑ in PVR or PCWP can → pulmonary hypertension (PH)
- *Pre-capillary PH*: PVR ≥2, PCWP ≤15, ↑DPG & TPG
- *Post-capillary PH*: PVR <2, PCWP >15, nl DPG & TPG
- *Mixed PH*: PVR ≥2, PCWP >15, ↑DPG & TPG

Transpulmonary gradient (TPG) = mPAP – PCWP; nl <12
Diastolic pulmonary gradient (DPG) = PA diastolic (PAd) – PCWP; nl <7

CLINICAL MANIFESTATIONS

S/Sx: nonspecific; 2y delay to dx in 20% (Chest 2011;140:19)
- Early: **DOE**, lethargy, **fatigue** (2/2 inadequate CO w/ activity
- Late: exertional CP, **syncope**, edema, anorexia, abdominal distention (secondary to progressive RV failure)
- Rare: cough, hemoptysis, hoarseness (Ortner's syndrome)

Exam: loud P2; ↑JVP, edema, ascites, TR murmur, R-sided gallop, parasternal heave (LSB), PA tap (L 2nd ICS), edema, hepatomegaly, ascites
Imaging: CXR w/ enlarged PA, RA, RV (↓retrosternal space on lat.), pruning of peripheral vessels; CT w/ PA/Ao diameter ≥1
ECG: normal vs signs of RV hypertrophy/strain: RAD, R/S >1 in V1, RBBB, P pulmonale in II (RAE)
TTE: TR peak velocity ≥2.8 (= RVSP >35mmHg), PA diameter >25mm; RVOT acceleration time<105ms, TAPSE <1.7 cm, RV dilation/hypokinesis, RV/LV>1, IVC>21mm

DIAGNOSIS (ERJ 2019;53:1801904)

- RHC: gold standard (may not be needed in all circumstances) ± **iNO vasoreactivity testing** (+ response = ↓mPAP ≥10 mmHg to reach mPAP ≤40 mmHg w/ ↑ or = CO; guides treatment in idiopathic PH)
- Evaluation for etiology:
  - TTE: eval for left HF (& whether severity explains PH)
  - RUQUS: Assess for portopulm HTN, portocaval shunt
  - PFTs, DLD-CT, polysomnography: chronic lung disease, OSA
  - CPET: determine etiology of exercise intolerance (cardiac vs pulmonary/PAH vs other)
  - V/Q scan: eval for CTEPH
  - Labs: NT-proBNP, BMP, LFTs, eval for systemic disorders in groups 1 & 5 (if not already known) – HIV, connective tissue diseases (ANA, RF/CCP, ANCA, Scl-70, Ro/La), schistosomiasis (if clinically appropriate), urine & serum toxicology

WHO CLASSIFICATION (6th World Symposium on PH: ERJ 2019;53:1801913; JACC 2013;62:D34)

Pre-Capillary			Post-Capillary
Group 1: Pulmonary Arterial Hypertension (PAH)	**Group 3: Lung disease and/or hypoxemia**	**Group 4: Pulmonary artery obstructions**	**Group 2: Left heart disease**
- **Idiopathic** (♀>♂) - **Heritable** (e.g. *BMPR2*) - **Drug/toxin-induced**: cocaine, anorexigens, etc - Associated with: **CTD** (MCTD, SSc, SLE), **HIV**, **portal HTN**, congenital heart disease, schisto - PAH long-term responders to CCBs - PVOD and/or pulm. capillary hemangiomatosis - Persistent PH of newborn	Obstructive: **COPD** Restrictive: **ILD** Mixed obstructive/restrictive Chronic hypoxia w/o lung disease: **OSA, OHS** Developmental lung dz (ERJ 2019;53:1801914)	**Chronic thromboembolic disease** (ERJ 2019;53:1801915) *NB*: only ~33-75% had known prior VTE. Occurs after ~4% of PEs (NEJM 2004;350:2257) Other PA obstructions: malig., arteritis w/out CTD, parasites, congenital PA stenosis	**HFpEF** **HFrEF** **Valvular disease** Congenital/acquired conditions (ERJ 2019;53:1801897)
Group 5: **Misc.** chronic hemolytic anemia (e.g., sickle cell), MPN, sarcoid, metabolic d/o, complex congenital heart disease			

WHO Functional Classes: Class I = asx w/ ordinary activity, II = sx w/ ordinary activity, III = sx w/ minimal activity, IV = sx at rest

MANAGEMENT

Treat underlying etiology: CTD, CHF, hypoxemia, VTE, etc. Advanced therapies (below): *guided by WHO functional class* (reserved for II-IV). **Most evidence in Group 1**. Surgery: pulmonary thromboendarterectomy (CTEPH), atrial septostomy (R→ L shunt), lung txp in select pts. General: exercise/pulm rehab, O_2, diuresis (in RHF), contraception required in ♀ (2 forms vs permanent form), vaccines

Mechanism	Medication		Indication	Side effects
Endothelin receptor antagonists	Bosentan, ambrisentan, macitentan	Blocks pulmonary vasoconstriction & proliferation	Group 1: ↓sx, ↑6MWT (NEJM 2002;346:896; Circ 2008;117:3010) Macitentan: ↓morbid/mortality (NEJM 2013;369:809)	Anemia, PNA, edema, hepatotox. Macitentan: also flu, HA, UTI, bronchitis
(NO)-cGMP enhancers	PDE5 inhibitors: sildenafil, tadalafil, vardenafil (not FDA approved for PAH)	Increases cGMP → vasodilation, blocks proliferation	Group 1 (sildenafil studied in some etiologies of Group 2 and 5): ↓sx, ↑6MWT (NEJM 2005;353:2148; NEJM 2009;361:1864)	Erythema, flushing, indigestion, HA, insomnia, epistaxis, rhinitis, retinal hemorrhage, *contraindicated if using nitrates
	sGC stimulator: riociguat		Group 1 & Group 4: ↓sx, ↑6MWT (NEJM 2013;369:330)	↓BP, n/v/d/const., GERD, anemia, dizziness, HA, hemorrhage
Prostacylin pathway agonists (PPA)	Analogues: epoprostenol, treprostinil, iloprost	Increase cAMP → vasodilation, blocks proliferation	Group 1: ↑6MWT, ↑QOL, ↓mortality w/ epo.; reserved for sickest patients. (NEJM 1996;334:296) Group 3: ↑6MWT, ↓NTpro w/ treprost. (NEJM 2021;384:325) Group 5: some etiologies	CP, ↓BP, ↑HR, flushing, abd pain, anorexia, n/v/d, MSK & jaw pain, dizziness, HA, hemorrhage
	Receptor agonist: selexipag		Group 1: ↓hospitalization; no Δ mortality (NEJM 2015;373:2522)	Diarrhea, nausea, jaw pain, HA, anemia
CCB (trial)	Nifedipine, diltiazem	Vasodilation	⊕ iNO vasoreactivity test, ⊘ RV failure	↓BP, LE edema

Initiating Therapy based on ERS/ESC risk stratification guidelines (ERJ 2015;46:903, ERJ 2022): *refer to Pulm HTN clinic*
Risk stratification criteria: WHO functional class, 6MWT, NT-proBNP, TTE/cMRI, RHC at dx, consider CPET
- Low/intermediate risk: dual oral therapy (target ERA/NO pathways; ambrisentan and tadalafil preferred). Can add CCB if vasoreactive.
- High risk: IV prostacyclin agonist (epoprostenol preferred) + ERA + PDE5i
- **Goal of therapy is to attain low risk criteria:** NT-proBNP < 300, WHO/NYHA class I or II, 6MWT>440m. May add IV/SQ prostacyclin if low risk criteria are not met 3-6mo after initiation of oral agents (ERJ 2017;50:1700889; ERJ 2022)

Matthew Adan

Pulmonary & Critical Care — Mechanical Ventilation

Indications for Intubation

- **Failure of NIPPV**: unable to tolerate, progressive hypoxemia/capnia, high pressures, ↓mental status, ↑fatigue/WOB
- **Poor ventilation**: $PaCO_2$ >60 with severe acidemia (COPD/asthma, sedation, neuromuscular disease, resp. muscle fatigue, trauma)
- **Poor oxygenation**: worsening P:F ratio (PNA, pulmonary edema, ARDS, PE)
- **Airway protection**: AMS/↓secretion management, shock, facial/head trauma, n/v/UGIB, severe bronchospasm/anaphylaxis, procedural necessity
- **Persistent increased work of breathing**: severe bronchospasm, airway obstruction, inability to compensate for severe acidemia
- **Hemodynamic instability**: unstable arrhythmia, severe shock

Call RICU for intubation: x6-3333

RICU will ask: **AMPLE**

A = allergies
M = medications (current)
P = past medical hx (incl. h/o LVEF and RV function, prior intubations or difficult airway)
L = last meal/K (succinylcholine can cause hyperK)
E = events (prompting intubation)

During intubation, have at bedside:
(1) Good access (2) IVF (3) sedative agent (e.g. propofol) (4) pressors (neo >> levo)

Hemodynamic Consequences of Intubation

- PPV ↑ intrathoracic pressure → ↓ LV & RV preload, ↑ PVR/RV afterload (variable) & ↓ LV afterload. Can precipitate RV failure in pHTN and RV dysfx
- In acidosis such as DKA, can be difficult to match RR to physiologic needs
- Vasoplegia and loss of compensatory tachycardia from sedatives ↓ sympathetic tone = ↓ BPs; have appropriate pressors ready

General Principles: (NEJM 2001;344:1986; Respir Care 2017;62:629)

Five main variables: (1) RR, (2) tidal volume (V_T), (3) FiO_2, (4) positive end-expiratory pressure (PEEP), (5) mode of ventilation

- **Ventilation determines P_aCO_2: ↓P_aCO_2 by increasing RR and/or V_T** (↑minute ventilation where MV = RR x V_T)
  1) RR: often adjust this first; avoid >RR 30-35 due to risk of inadequate expiratory time → air trapping/auto-PEEP
  2) V_T (often set at ≤6cc/kg IBW): when ↑, ensure P_{plat} ≤30 & driving pressure (ΔP = P_{plat} – PEEP) ≤15 to minimize lung injury
- **Oxygenation: ↑PaO_2 by ↑FiO_2 and/or PEEP**
  3) FiO_2: avoid FiO_2 >0.6 for prolonged periods due to oxygen toxicity
  4) PEEP: if recruitable lung present, ↑PEEP will ↑alveolar recruitment, improve V/Q match and compliance → ↑P:F & P_{drive} stable/↓; if ↑PEEP → no Δ/↓ P:F, ↑P_aCO_2, or ↑P_{drive}, lung is not recruitable & ↑PEEP = ↑dead space/↓compliance due to overdistention

Ventilator Modes: (Respir Care 2007;52:301)

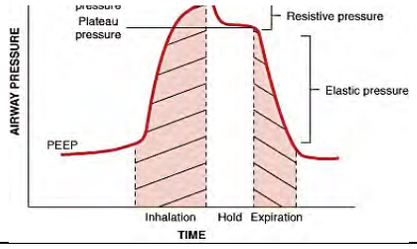
MODE	SET *Indep. Var.*	MEASURED *Dep. Var.*	PROS/CONS	HOW TO READ	WHEN TO USE
AC/VC *Assist Control/Volume Control: delivers a breath until set tidal volume is reached*	**V_T** PEEP RR FiO_2 I:E or flow	PIP & P_{plat} I:E or flow	☺: ↑control (fixed V_T prevents barotrauma or atelectrauma) ☹: fixed insp. flow regardless of effort, ↑dyssynchrony	"Pt is on Volume Control w/ V_T of 400 (4cc/kg), set at a rate of 16 breaths/min, PEEP of 8, and FiO_2 0.6; breathing at set rate of 16 (or over) with V_T ~400 for MV of 6.4L"	- Acute resp failure - ARDS - Airflow limitation (e.g. COPD, asthma)
AC/PC *Assist Control/Pressure Control: delivers a breath until set pressure is reached*	**P_{insp}** PEEP RR FiO_2 I:E	Flow V_T	☺: variable flow (& V_T) during inspiration to satisfy pt demand, ↓dyssynchrony ☹: can cause volutrauma as compliance or pt effort changes	"Pt is on Pressure Control of 18 (P_{insp}) over 5 (PEEP), set at a rate of 16 breaths/min, and FiO_2 0.3; breathing V_T ~400, at set rate of 16 (or over) for a MV of 6.4L."	- Air leak (e.g. PTX) - May trial in situations of vent dyssynchrony
PSV *Pressure Support Ventilation: delivers set pressure triggered by patient's spont breaths*	P_{insp} PEEP FiO_2 RR (backup)	I:E Flow V_T RR	☺: better tolerated, less sedation, trial pre-extubation (e.g. SBT on 0/0 or 5/5) ☹: ↓control over parameters, volutrauma possible, no fixed RR (only backup)	"Pt is on Pressure Support of 10 (P_{insp}) over 5 (PEEP) with an FiO_2 0.3; breathing V_T of ~500 at 20 breaths/min. for a MV of 10L."	- Intubated for non-cardiac or lung failure (e.g. AMS) **- Weaning vent** - Severe met acidosis

Monitoring Mechanics

Parameter	Target	Evidence
Tidal Volume (V_T)	ARDS: 4-8 cc/kg PBW Non-ARDS: 6-8 cc/kg PBW	ARDS: V_T 6cc/kg had ↓mortality and vent-free days vs 12cc/kg (NEJM 2000;342:1301) Non-ARDS: V_T 10cc/kg vs 4cc/kg ← no Δ mortality or vent-free days (JAMA 2018;320:1872)
Plateau pressure (P_{plat}) Driving pressure (ΔP = P_{plat}-PEEP)	<30 <15	ARDS: ↓driving pressure a/w ↑survival (NEJM 2015;372:747) Non-ARDS: driving pressure not a/w 30d mortality (Crit Care 2019;23:424)
Compliance (V_T/ΔP) Airway Resistance (PIP-P_{plat})	>50 <10	Maximizing O_2 transport and minimizing dead-space occurred at the **greatest total static compliance** (NEJM 1975;292:284)

Ventilator Maneuvers for Monitoring Mechanics

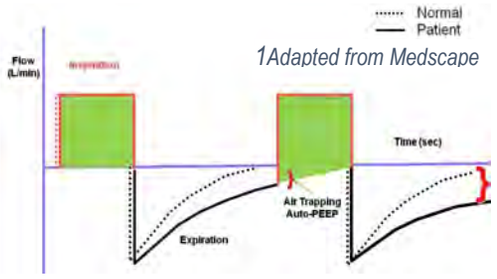
- *Inspiratory hold*: end inspiratory pause; measure P_{plat} → calculate ΔP, airway resistance, compliance
- *Exp hold*: end expiratory pause; quantifies autoPEEP
- *$P_{0.1}$*: measures resp drive w/ neg pressure generated by occluded insp, indep of muscle weakness, C, R



Pulmonary & Critical Care — Mechanical Ventilation

VENTILATOR COMPLICATIONS

- **Dynamic hyperinflation (auto-PEEP)**: measured by end expiratory hold. Auto PEEP = end exp pressure – set PEEP
  - Diagnosis: end-expiratory flow >0 due to incomplete alveolar emptying
  - RFs: vent strategy causing hyperinflation (high RR, ↑I:E ratio) or obstructive disease (asthma, COPD, CF)
  - Consequences: adverse hemodynamic effects (HoTN secondary to ↓venous return), alveolar over-distention (→ volu-/barotrauma); ↑effort to trigger breath
  - Tx: longer exhalation (↓I:E ratio, ↓RR), set exogenous PEEP to 2/3 auto-PEEP, bronchodilators for obstruction
  - If severe hemodynamic or resp. compromise, transiently **disconnect pt from ventilator** and manually bag ventilate to allow deflation



↑Adapted from Medscape

- **Ventilator-induced lung injury (VILI)**: alveolar injury →↑alveolar permeability, interstitial & alveolar edema, alveolar hemorrhage, hyaline membranes, & alveolar collapse (similar to ARDS) (NEJM 2013;369:2126). Avoid w/ lung protective ventilation (see *ARDS*).
  - **Volutrauma**: over-distension of alveoli due to high V_T; or, if there is heterogenous consolidation or atelectasis, a disproportionate volume from each breath is delivered to open alveoli
  - **Atelectrauma**: shear forces from cyclic alveolar recruitment and de-recruitment injure adj alveoli/airways
  - **Biotrauma**: cytokine release from lung epithelium → multi-organ dysfunction
  - **Oxytrauma**: ↑FiO_2 →free radical production, lung injury
  - **Barotrauma**: injury from high P_{plat} (highest risk >35) → PTX, subcutaneous emphysema, pneumomediastinum
- ↑ **Peak inspiratory pressure (PIP)** = airway resistance + elastic resistance (P_{plat}). To troubleshoot, determine P_{plat} with insp. hold
  - If normal P_{plat} (<30): ↑airway resistance: bronchospasm, secretions/mucus plug, ET malposition/kink/biting, airway edema
  - If elevated P_{plat} (>30): ↑elastic pressure = ↓compliance
    - Decreased functional lung size/overdistention: auto-peep, atelectasis, R main stem, ARDS, PNA, DAH, pulm edema
    - Increased thoracic pressure: obesity, kyphosis, burns, abdominal compartment/ascites, effusions, PTX, Tberg position
    - Parenchymal disease: ILD, post radiation
  - Low PIP? leak in the system: bronchopleural fistula, ET cuff rupture/dislodge, tubing damage
- **Other complications**: VAP, laryngeal edema, tracheal stenosis, PTX

ALGORITHM FOR RESPIRATORY PLAN (REMIX)

R	Reason for intubation	ARDS, PNA, COPD, pulmonary edema, aspiration, hypoventilation, altered mental status, etc
E	Exchange (gas exchange)	Recent ABG; plan to improve PaO_2 (i.e. diuresis, pulmonary vasodilators) and/or PCO_2 (i.e. #RR)
M	Mechanics	P_{plat}, PIP, resistance pressure, elastic pressures; chest wall/respiratory muscle strength
I	ID/infection	Sputum cx data, abx day #, source control, need for bronchoscopy; assess for VAP
X	eXtubation barriers	Daily SAT/SBT, secretion clearance, mental status, planned procedures
(S)	Sedation	Current sedation, whether Δ needed e.g. start dexmedetomidine/quetiapine as bridge peri-extubation

LIBERATION & EXTUBATION: (ATS/CHEST: AJRCCM 2017;195:115; Chest 2001;120:375S; NEJM 2012;367:2233; ERJ 2007;29:1033)

- **Requirements for extubation**:
  (1) adequately treated underlying disease and hemodynamic stability
  (2) adequate oxygenation and ventilation: PaO_2/FiO_2 ≥150-200, PEEP ≤5-8, FiO_2 ≤0.4-0.5, pH >7.25
    - **Rapid Shallow Breathing Index (RSBI) = RR/V_T**; RSBI >105 predicts extubation failure (Sn>Sp) (NEJM 1991;324:1445)

  (3) ability to cough/manage secretions (ideally alert/following commands, but if protecting airway, AMS does not preclude extubation)

  (4) +cuff leak. Absence of cuff leak is concerning for laryngeal edema → consider methylpred 20mg IV q4h 12hrs prior to extubation or IV methylpred 40mg x1 4hrs prior or IV dexamethasone 5mg q6h (Eur J Anaesthesiol 2010;27:534).
- **Liberation protocol**: daily **Spontaneous Awakening Trial (SAT)** + **Spontaneous Breathing Trial (SBT)**
  - **SAT**: ↓ ventilator time, ICU LOS, & mortality if paired with SBT (NEJM 2000;342:1471; Lancet 2008;371:126)
  - **SBT**: ~30-120min daily trials w min support (PEEP ≤5 on PSV)=↓ vent time (NEJM 1996;335:1864; NEJM 1995;332:345)

    Ways to fail: hypoxemia (SaO_2 <90%, PaO_2<60), hypercarbia ($PaCO_2$ ↑ by >10), low V_T, respiratory distress (↑HR, ↑RR, HTN, accessory muscle use, diaphoresis), arrhythmia, hemodynamic instability, anxiety/agitation, somnolence

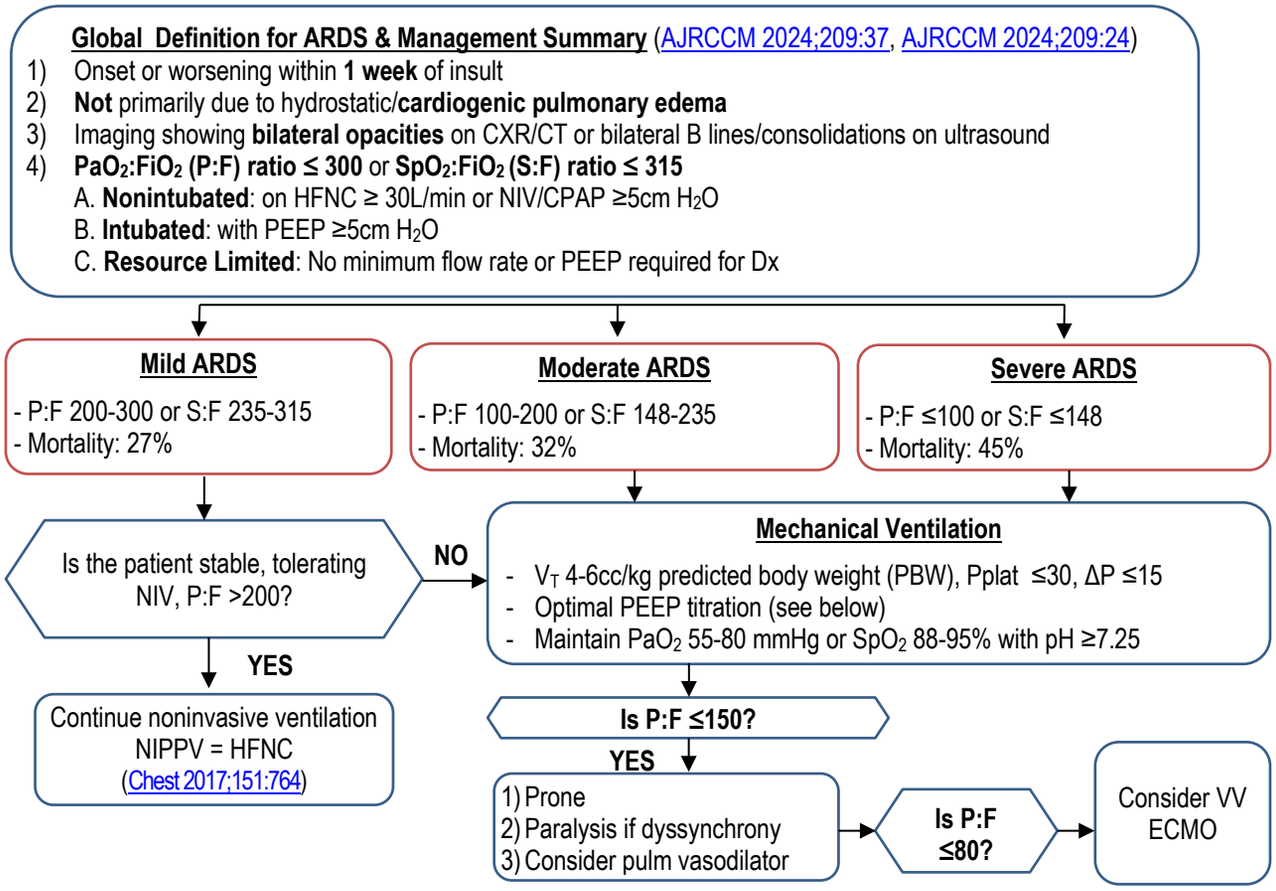
    Causes of SBT failure: underlying etiology not corrected, volume overload, cardiac dysfunction, neuromuscular weakness, delirium, anxiety, metabolic abnormalities
- **Extubation strategies**:
  - Extubation to **NIPPV or HFNC** in patients with hypercarbia / risk factors for reintubation, not done routinely → ↓ post-extubation respiratory failure (Lancet 2009;374:1082; JAMA 2016;316:1565). HFNC w/ intermittent NIV post-extubation → ↓ reintubation compared to HFNC alone (JAMA 2019;322:1465).
  - If **agitation** is limiting ability to extubate, consider dexmedetomidine → may improve odds of extubation (JAMA 2009;301:489)
- **Post-extubation respiratory failure**: due to poor secretion clearance, CHF, aspiration, bronchospasm, laryngeal edema
  - *NB*: no benefit to NIPPV as rescue therapy during post-extubation respiratory failure and may be associated w/ worse outcomes (NEJM 2004;350:2454). Not recommended per ERS/ATS guidelines (ERJ 2017;50).
- **Tracheostomy:** usually performed once intubated for 14-21 days. Early tracheostomy (7 days) if expect intubation >14 days → ↑comfort, allows ↓ sedation, ↓ risk of tracheal stenosis, ↓ vent-free and ↓ ICU days, though no change in VAP rate (JAMA 2010;303:1483; Crit Care 2015;19:424; Br J Anaesth 2015;114:396)

Pulmonary & Critical Care

ARDS

PATHOPHYSIOLOGY OF ARDS

Direct lung injury: pneumonia, aspiration, inhalational injury, near drowning, pulmonary contusion; **indirect lung injury**: sepsis, trauma, pancreatitis, drugs, burns, cardiopulmonary bypass/pump, transfusion-related acute lung injury (TRALI)
Ddx (ARDS Mimics): Eosinophilic PNA (AEP), acute interstitial PNA (AIP), organizing PNA
Pathway: diffuse, immune-mediated lung injury causing pulmonary capillary and alveolar epithelial damage leading to increased vascular permeability, impaired gas exchange, and decreased lung compliance (NEJM 2017;377:562)


Global Definition for ARDS & Management Summary (AJRCCM 2024;209:37, AJRCCM 2024;209:24)
1) Onset or worsening within 1 week of insult
2) Not primarily due to hydrostatic/cardiogenic pulmonary edema
3) Imaging showing bilateral opacities on CXR/CT or bilateral B lines/consolidations on ultrasound
4) PaO2:FiO2 (P:F) ratio ≤ 300 or SpO2:FiO2 (S:F) ratio ≤ 315
A. Nonintubated: on HFNC ≥ 30L/min or NIV/CPAP ≥5cm H2O
B. Intubated: with PEEP ≥5cm H2O
C. Resource Limited: No minimum flow rate or PEEP required for Dx
Mild ARDS
- P:F 200-300 or S:F 235-315
- Mortality: 27%
Moderate ARDS
- P:F 100-200 or S:F 148-235
- Mortality: 32%
Severe ARDS
- P:F ≤100 or S:F ≤148
- Mortality: 45%
Is the patient stable, tolerating NIV, P:F >200?
NO
YES
Continue noninvasive ventilation
NIPPV = HFNC
(Chest 2017;151:764)
Mechanical Ventilation
- VT 4-6cc/kg predicted body weight (PBW), Pplat ≤30, ΔP ≤15
- Optimal PEEP titration (see below)
- Maintain PaO2 55-80 mmHg or SpO2 88-95% with pH ≥7.25
Is P:F ≤150?
YES
1) Prone
2) Paralysis if dyssynchrony
3) Consider pulm vasodilator
Is P:F ≤80?
Consider VV ECMO

MANAGEMENT PRINCIPLES IN ARDS: (ATS/ESICM/SCCM: AJRCCM 2017;195:1253)

	Strategy (in order of decreasing level of evidence)	Effects
Low Tidal Volume Ventilation (LTVV) (NEJM 2007;357:1113) (NEJM 2000;342:1301)	• **Maintain oxygenation** while **preventing ventilator-induced lung injury** (VILI) • VT 4-6 cc/kg PBW w/ goal Pplat ≤30, driving pressure (Pplat-PEEP) ≤15 o May allow ↑Pplat if ascites, obesity, etc. as may not accurately reflect transpulmonary pressure (see "esophageal balloon catheter" on next page) • Permissive hypercapnia: pH goal ≥7.20-7.25 permits lower VT to minimize VILI o *Contraind*: ↑ICP, RV fail./PH (↑pulm. vasoconst.), TCA/ASA o/d, pregnant	**↓mortality** (31% vs 39.8%) and ↑vent-free days vs "traditional" VT (12 cc/kg, Pplat <50)
Prone Positioning (PROSEVA NEJM 2013;368:2159) (Chest 2023;163:533)	• Initiate within 36h in pts with P:F<150 on FiO2≥0.6, PEEP≥5cmH2O • ↓V/Q mismatch by ↓compressive atelectasis from heart & diaphragm → more homogenous vent. → ↑alveolar recruit. → ↓regional volutrauma & ↑compliance • *Contraind.*: hemodynamic instability, ↑ICP, inability to turn neck (fixed/unstable C-spine), 2/3rd tri. pregnancy, recent sternotomy	**↓mortality** (28d & 90d) in mod/severe ARDS
Conservative Fluid Management (NEJM 2006;354:2564)	• Minimize pulmonary edema, avoid ⊕ fluid balance after reversal of shock • Dynamic assessment of volume responsiveness (i.e. pulse pressure variation, passive leg raise) (CCM 2017;45:1538) • FACTT Trial: CVP<4 (conservative) vs. CVP ≤10-14 (liberal)	↓ICU LOS & vent-free days, no Δ in 60d mortality or AKI
Positive End-Expiratory Pressure (PEEP) (NEJM 2004;351:327) (JAMA 2010;303: 865)	• Maximize recruitment, minimize trauma from cyclic atelectasis • Higher PEEP distributes VT over more alveoli → less over-distention → improves oxygenation (via ↓V/Q mismatch and ↓shunt fraction) & compliance • CV effects of PEEP: ↓preload/SV, RV afterload varies, ↓LV "afterload", ↓BP • Harms of PEEP: barotrauma, ↑dead space, hemodynamic effects	No clear mortality benefit. Possible benefit for ↑PEEP if P:F ≤200
Neuromuscular Blockade (ROSE NEJM 2019;380:1997) (AJRCCM 2024;209:24)	• ↑oxygenation and ↓VILI by ↓vent dyssynchrony and chest wall compliance • No survival benefit to routine early paralysis for mod-severe ARDS (P:F <150) as compared to light sedation, possible mortality benefit when used for vent synchrony or in early severe ARDS when deep sedation is otherwise required • Can use as bolus/infusion to maintain vent synchrony in mod-severe ARDS	possible ↓mortality & ↑vent free days when used for synchrony **Risk:** ↑ICU-acquired weakness

Kristy Abo

SUMMARY OF RESCUE THERAPIES FOR HYPOXEMIA (6 P's of refractory hypoxemia)

- Pee: consider diuresis to reduce pulmonary edema (see "conservative fluid management" above)
- PEEP: optimize PEEP (see "PEEP" below)
- Prone positioning: should be implemented *early* (12-24h) if P:F <150 (or 200) despite optimal PEEP titration
  - Maintain prone ≥16h. If supinate and P:F remains >150 (or 200) and ΔP ≤15 after 2h, can remain supine
- Pulmonary vasodilators: start with iNO trial (40ppm; up to 80ppm); if effective, use inhaled epoprostenol (Veletri)
  - Should see at least 20% ↑PaO_2, otherwise do not continue therapy due to cost and risks, including hypotension
  - ↓V/Q mismatch by selectively dilating vessels that perfuse well-ventilated lung; also ↓PVR and ↓RV afterload
  - No mortality benefit and ↑risk of renal failure, but may improve oxygenation in first 24h and total lung capacity at 6mo (Cochrane Rev 2016; Crit Care 2012;16:R36). *NB*: risk of methemoglobinemia w/ iNO, inhaled pulmonary vasodilators exhibit tachyphylaxis
- Paralysis: can be used to maintain vent synchrony (see "neuromuscular blockade" above), esp. when double triggering – permits maintenance of LTVV. Now also conditionally recommended in early ARDS (<48h) w/ P:F <100 if already under deep sedation. Start w/ intermittent boluses & transition to infusion if persistent dyssynchrony >3 boluses/2h (cisatracurium 0.1-0.2mg/kg q30min PRN → 0-5mcg/kg/min; rocuronium 0.6-1.2mg/kg q30-60min PRN → 0-20mcg/kg/min, start at 8-12mcg/kg/min). Do NOT wean sedation while under blockade (RASS goal -5 prior to initiation). Monitor depth of sedation with BIS (target 40-60)
- Perfusion (ECMO): for severe, refractory hypoxemia with P:F ≤ 80 +/- hypercarbia w/ pH <7.25 and pCO2 >60; see *ECMO*

LUNG PROTECTIVE (ARDSNET) VENTILATION

- **Initial ventilator set-up**: V_T = 6 cc/kg PBW, RR to approximate baseline MV (RR <35), moderate PEEP (8-10)
- **Adjustments**: (also see *Mechanical Ventilation*)
  - Oxygenation: goal **PaO_2 55-80 mmHg** or **SaO_2 88-96%**
    - OX-ICU raised concern hyperoxia leads to ↑mortality. However, recent studies demonstrate equipose without clear beneficial target (ARJCCM 2021, PILOT)
      - If persistent hypoxemia requiring FiO_2 >~0.6, optimize PEEP (see below)
  - Mechanics: goal **plateau pressure** (**Pplat**) **≤30** & **driving pressure (ΔP) ≤15** (obtain with inspiratory hold)
    - If Pplat >30 and/or ΔP >15: ↓V_T by 1 cc/kg PBW (minimum V_T 4 cc/kg PBW); limit on ability to ↓ is ↓MV → ↑pCO_2 & ↓pH
    - If Pplat <25 and V_T <6cc/kg PBW: can ↑V_T by 1 cc/kg until Pplat >25 or V_T 6 cc/kg PBW
  - pH: goal **7.20-7.25 to 7.45** ("permissive hypercapnia" unless contraindicated, lower boundary context dependent)
    - pH below goal: ↑RR (up to 35/min) until pH at goal or $PaCO_2$ <25; watch for auto-PEEP development at high RR
    - If RR = 30-35/min & pH goals not met: can ↑V_T (may cause ↑Pplat >30)

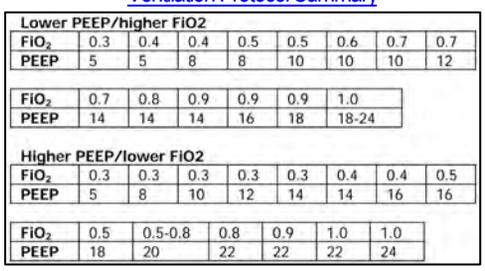
Mechanical Ventilation Goals in ARDS

Measure	Goal
Oxygenation	PaO_2 55-80mmHg SaO_2 88-96%
Mechanics	Plateau pressure (Pplat) ≤30 Driving pressure (ΔP) ≤15
pH	7.20-7.25 to 7.45

OPTIMAL PEEP FOR ARDS

- **ARDSNet FiO_2/PEEP scale**:
  - If P:F <150 w/ PEEP 5cm H_2O, assess ability to recruit lung by increasing PEEP from 5 → 15cm H_2O
  - If improvement, use ARDSNet high PEEP/low FiO_2 scale; if no improvement, use low PEEP/high FiO_2 scale (see right)
- **Best PEEP trial**: select the PEEP corresponding to best global recruitment with lowest risk for overdistention based on **resp system compliance (C_{RS} = V_T / [Pplat - PEEP])**
  - Keep V_T constant and use **decremental titration of PEEP**; choose best PEEP based on balance of highest compliance, lowest driving pressure (<15), Pplat <30, acceptable oxygenation, and stable hemodynamics
- **Driving pressure**: ΔP = Pplat - PEEP (goal: ≤15)
  - Represents the relationship between tidal volume and lung compliance (ΔP = V_T/C_{RS})
  - Lower ΔP associated with ↑**survival** independent of other variables (V_T, PEEP, Pplat) (NEJM 2015;372:747)
- **Recruitment maneuvers** (if hemodynamically stable):
  - Used to open collapsed alveoli to ↓tidal opening and closing (**atelectrauma**) and ↑participation in gas exchange
  - Begin with **high PEEP** to open up alveoli, then decremental PEEP titration to optimize mechanics (JAMA 2008;299:637)
  - Outcomes are mixed w/ ↑ (JAMA 2017;318:1335) and ↓mortality (low quality, Cochrane Rev 2016); **avoid** ↑↑↑PIPs (>50)
  - Strong recommendation **against** prolonged lung recruitment maneuvers in moderate-severe ARDS (AJRCCM 2024;209:24)
- **Esophageal balloon catheter**: estimates intrapleural pressure; used to calculate **transpulmonary pressure** (**P_{tp}** = alveolar pressure [Pplat] - intrapleural pressure). PEEP then titrated to maintain optimal P_{tp} (<25 at end-inspiration to prevent VILI, 1-2 at end-expiration to prevent atelectrauma) (NEJM 2008;359:2095)
  - No effect on mortality, ventilator free days, or ICU days, despite improved oxygen and lung compliance, but ↓risk of needing advanced rescue therapy (JAMA 2019;321:846)
  - Consider in cases of high intra-abdominal pressure (e.g., obesity, ascites, abdominal compartment syndrome)

NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary



Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

STEROIDS FOR ARDS

- For indication & use in COVID-19, see MGH guidance (directory in Handbook), RECOVERY trial (NEJM 2021;384:693)
- Non-COVID-19 ARDS: suggested in ARDS but optimal regimen unknown (conditional rec, moderate certainty) (AJRCCM 2024;209:24) and there are conflicting data; Dexa-ARDS (Lancet RM 2020;8:267) → ↑ventilator-free-days & ↓mortality in mod-severe ARDS. Other trials: possible benefit in early mod-severe ARDS, ↑mortality if ARDS ≥14d (Chest 2007;131:954; NEJM 2006;354:1671)

Pulmonary & Critical Care

ECMO

TYPES OF ECMO (JACC 2014;63:2769)

To call ECMO consult:
- MGH STAT App
- Directory: type "ECMO Consult" or **p24252**
857-310-0335

1. **Venoarterial** (*VA*, **replaces heart and lungs**): primarily cardiogenic shock
   - Venous blood is removed, oxygenated, CO_2 extracted, and reinfused in arterial system
   - Venous cannula in com. femoral vein (drainage from IVC or RA); arterial cannula in R fem. artery
2. **Venovenous** (*VV*, **replaces lungs**): manages hypoxemic resp. failure; relies on native cardiac output
   - Venous blood is removed, oxygenated, CO_2 extracted, and reinfused in venous system
   - Either two venous cannulae (common fem. vein and SVC) or a bicaval dual lumen single cannula via R IJ that allows for mobility

Indications:	**Contraindications**:
• Reversible acute resp failure (VV): *e.g. ARDS, bridge to transplant or recovery* PaO_2/FiO_2 <80 despite optimization, unable to achieve safe inflation pressures (Pplat <30), CO2 retention (pH<7.25 w/ PCO2 > 60) with inability to mechanically ventilate. See ELSO. • Reversible cardiogenic shock (VA): *e.g. PE, cardiac arrest.* Refractory low cardiac index (<2L/min/m²) & HoTN despite adequate volume, inotropes, & IABP. ECPR. • Bridge to definitive therapy (transplantation, VAD, recovery)	• Absolute (VA or VV): non-recoverable multi-organ failure/neurological disease; unwitnessed arrest/CPR >30min w/o ROSC; active severe bleeding; contraindication to AC, recent NSGY procedure/active intracranial bleed (<10d) • Absolute VA: BMI>40; AoD; severe AI; ESLD/ESRD • Absolute VV: severe right or left HF • Relative: age>70; multi-organ failure; severe pHTN; unknown neuro status; GVHD; active cancer; immunosuppression; ventilated >7d; DIC; survival <30% (via RESP and SAVE scores)

ECMO VARIABLES

Drainage Cannula in large central veins (IVC, SVC, or RA) || Return Cannula in RA or Ao (depending on configuration)

- **Sweep** (aka gas flow, replaces ventilation (L/min)): ↑sweep → ↓P_aCO_2 in blood returning to pt therefore ↑sweep requirements = worsening ventilation vs ↑ **CO_2 production** (fever, infxn, renal failure). Controls O2 delivery if any. When sweep is weaned off or "capped" in VV-ECMO, ECMO support for ventilation / oxygenation is also off.
- **FdO_2** (fraction *delivered* **O2 in sweep gas flow**): Generally set at 1.0
- **RPM**: Predominant determinant of **blood flow** (2-5L/min; >7LPM limited by membrane lung efficiency also affected by cannula size & native CO). VV ECMO – based on BSA to estimate O_2 consumption (BMI may limit candidacy), partially weaned. VA ECMO – indicates % of CO support from ECMO, main weaning variable.
- **Transmembrane Pressure** (dP or ΔP = P_{pre} - P_{post}): reflects oxygenator (membrane) function, trended daily
  - ↑ ΔP: check membrane for clots and ABG to assess impact on gas exchange. Check RPM (ΔP = BF x R so may reflect ↑ flow).
  - ↓ ΔP: check ECMO circuit for kinks either at the inflow or outflow sites
- **AC**: UFH, follow PTT, Xa, AT-III. Goals: d/w attending/pharmacist
- **Mechanical Ventilation**: Pt may be placed on PC with low Pinsp to enable "lung rest." Increasing spontaneous TV reflects improvement in lung function/ability to wean circuit. Once lung function improved, wean sweep to assess ability to ventilate endogenously, and from there can attempt to wean off VV-ECMO Surg Clin North Am 2022;102:23

COMPLICATIONS (Heart Lung Circ 2014;23:10)

- **ECMO: clots** (oxygenator, pump, tubing, hemofilter; 0.13-22%); **cannula displacement** (0.8-8%); **air embolism, oxygenator failure, pump failure. For emergencies, STAT page ECMO team.**
- **Patient: bleeds** (access sites, ENT/Pulm/GI/GU, intracranial, hemolysis, DIC; 5.3-79%); **neuro** (ICH, stroke, seizure, encephalopathy; 10-33%); **limb ischemia** (13-25%); **infxn** (17-49%; to help minimize this risk NO additional access placed after ECMO placed- all labs drawn off circuit); **AKI** (30-58%); **multi-organ failure** (10%); **cannular** (4.8%)

TROUBLESHOOTING THE CIRCUIT

- **Baseline lab goals**: Hgb >7.5g/dL; plt >75K; fibrinogen >150; active T&S. Maintain SpO_2 > 85% and PaO2 > 55.
- **Chatter**: shaking/sound caused by ↑⊖pressure in tubing; can be due to **venous collapse**, **hypovolemia, thrombosis, tamponade, other cause of ↓CO, straining, kinking**. Tx: volume resuscitation (usually albumin), ↓ RPMs, cannula and/or repositioning
- **Hypoxemia** (as measured on **patient ABG or sats**):
  a) Recirculation: blood travels from the outflow (return) catheter back into the inflow (drainage) catheter, bypassing body. Can be NL if <25 % recirculation. If >25% or ↑ consider catheter malposition. Dx: unexplained ↑inflow O_2 sat, BRB in drainage catheter Tx: reposition cannula (10 cm apart) or switch to dual lumen cannula, ↓RPM
  b) Membrane failure: often due to excessive and/or abnormal clots/fibrin Dx: visual inspection of circuit with worsening hypoxemia on outflow sat/ABG (PaO_2<200 on 100% F_dO_2) or ↑ΔP by 20 in 4hrs Tx: replace membrane
  c) Shunt: occurs if native CO >> ECMO flow or w/ improving native CO (larger % of blood never travels through ECMO circuit and is poorly oxygenated) Dx: hypoxemia on pt ABG/sats. Tx: ↑RPM to ↑flow. To ↑ CO: ↓fever, ↓inotropes, ßB, CCB, phenylephrine
- **Harlequin (North-South) syndrome** (VA only): **hypoxia of upper extremities R worse than L, heart, brain** – can occur only when fem. artery cannulated. Cardiac recovery, but poor lung fx → native CO (deoxygenated) pushes against oxygenated ECMO blood in aortic arch leading to hypoxia of UE, brain, heart. Dx: low sats on R arm but normal sats on L (need R radial art line in VA ECMO) Tx: add a venous return cannula/transition to V-AV ECMO (Heart Lung Ves 2015;7:320)

OUTCOMES

- **Acute respiratory failure**: 2 major studies show ↓mortality, but unclear if from referral to ECMO center or ECMO itself: CESAR: (Lancet 2009;374:135) & EOLIA: (NEJM 2018;378:1965) with similar mortality in COVID-19 ARDS Lancet 2020;396:1071)
- **Refractory cardiogenic shock**: ~40% discharge survival; time CPR→ECMO = best death predictor (CCM 2008;36:1404; ASAIO 2017;63:60)

ECPR: ECMO as extension of CPR in cardiac arrest. In-hospital cardiac arrest: ↑survival (OR: 0.17) compared to CPR (CCM 2011;39:1); OHCA; no difference between 30d outcomes with ECLS vs traditional therapy for out-of-hospital cardiac arrest (NEJM 2023;388:299) and MI related cardiogenic shock (NEJM 2023;389:1286). Consider calling ECMO team if nearing 10 minutes w/o ROSC to discuss VA ECMO

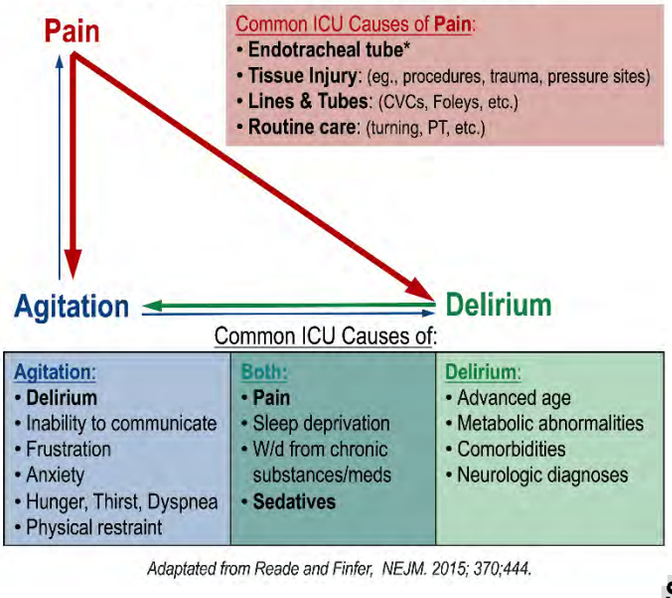
Pulmonary & Critical Care

Sedation

GOAL OF ICU SEDATION: addressing ICU triad of pain, agitation, & delirium (NEJM 2014;370:444)

1. **Pain**: common, ↑energy expenditure; analgesia alone adequate in some (Lancet 2010;375:475)
2. **Agitation**: target light sedation in intubated pts; no benefit to non-sedation (NEJM 2020;382:1103)
3. **Delirium**: 16-89% ICU pts; a/w worse mortality, QOL, cognitive outcomes (NEJM 2014;370:444); ↑risk w/ deep sedation, BZD use (Intensive Care Med 2007;33:66; JAMA 2007;298:2644)

ICU Triad of Pain, Delirium, and Agitation



Adaptated from Reade and Finfer, NEJM. 2015; 370;444.

RASS (Richmond Agitation Sedation Scale) (AJRCCM 2002;166:1338)		
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube/catheters; aggressive
+2	Agitated	Frequent, non-purposeful mvmt; fights ventilator
+1	Restless	Anxious, but mvmt not aggressive or vigorous
0	Alert & calm†	
-1	Drowsy†	Sustained awakening to voice (≥10sec)
-2	Light sedation	Briefly awakens w/ eye contact to voice
-3	Mod. sedation	Mvmt or eye opening to voice but no eye contact
-4	Deep sedation	Mvmt/opens eyes to physical stimulation but not voice
-5	Unarousable	No response to voice or physical stimulation
†Goal for most pts w/o indication for deep sedation		

A2F Bundle ↓mortality ↓delirium (Crit Care Med 2019;47:3)	
A	**A**ssess, Prevent, and Manage Pain
B	**B**oth Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT)
C	**C**hoice of analgesia and sedation
D	**D**elirium: Assess, Prevent, and Manage
E	**E**arly Mobility
F	**F**amily engagement and empowerment

SEDATION AGENTS (SCCM: CCM 2018;46:e825)

Sedative-Hypnotics (Non-Benzodiazepine)

Propofol: GABA agonist Dose: 5-50 µg/kg/min (Max 83)

1st line Sedative. Earlier extubation, ↓ICU LOS, & ↓mortality vs BZDs (AJRCCM 2014;189:1383)

Onset/Duration: **Fast on** (30-60sec) **Easily titratable**. **Often rapid awakening but has "context-sensitive" $T_{1/2}$** d/t ↑ lipid solubility. **Duration prolonged by 1) long infusion time, 2) ↑BMI, 3) adv. liver failure** (hepatic metab.; still 1st line in ESLD)

Analgesia: **None**

Respiratory: Powerful resp. depressant → cannot use w/out ETT outside an OR.

CV: Powerful vasodilator & direct cardiac depressant →↓↓**BP and ↓HR**

- ↓ICP & anti-seizure effects → **use in EtOH w/d & status epilepticus**.
- Monitor TGs with prolonged use. TG > 500 → risk of pancreatitis
- Propofol Infusion Syndrome: Rare. ↑ Risk if >48h of gtt, ↑infusion rate. Rhabdo, AGMA, ↓HR, LV dysfxn, HSM, Liver/Renal failure

Dexmedetomidine (Precedex): α_2-agonist Dose: 0.2-0.7 µg/kg/min (Max 1.5)

Use as Early Adjunct: ↓delirium & earlier extubation (JAMA 2016;315:1460) (Has EEG pattern most similar to natural sleep). (Anesthesiology 2015;123:937).

Onset/Duration: **Slow on** (5-10min, peak 15-30min). **Slow off** (>1-4hr). Therefore, less versatile & less titratable vs. propofol.

Analgesia: **Mild,** unclear mechanism (**use as adjunct, not primary analgesic**).

Respiratory: Less resp. depression vs. other hypnotics → **OK for non-intubated patients in monitored setting** (e.g., the ICU).

CV: Strong **negative chronotropy,** dose-limiting SEs = ↓HR & high-grade AVNB. Less vasodilation/↓BP vs. propofol; but can see w/d & **rebound HTN** if abrupt d/c.

- Falsely **low** BIS (interpret with caution in paralyzed patients)
- **Precedex Fever**: idiosyncratic high-grade fever, resolves w/ drug d/c.

Ketamine: NMDA-antagonist Dose: 5-30 µg/kg/min

Onset/Duration: **Fast on** (30-60sec). **Slow off** 2.5hrs; accumulates in renal/liver failure

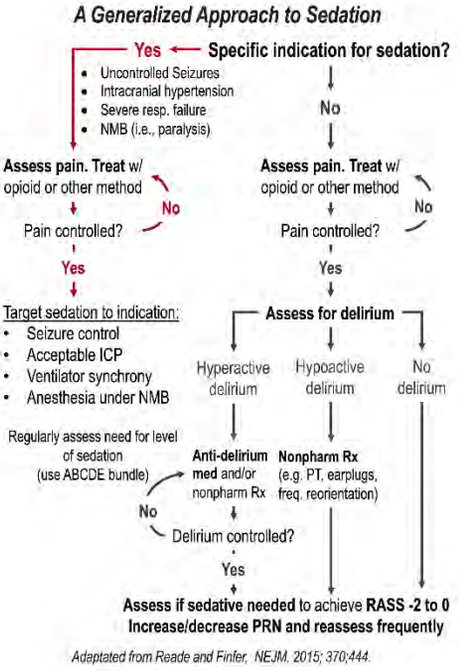
Analgesia: **Clinically relevant analgesia** via anti-NMDA; synergistic w/ opioids.

Respiratory: **Minimal Resp. depression**. Bronchodilatory. ↑**Secretions**: caution peri-/post-extubation

CV: ***Indirect*** **sympathomimetic:** ↑HR + ↑BP in early illness/stable pts.
Direct negative **inotrope:** ↓BP in extremis/↓cardiac reserve (no longer offset by endogenous catecholamine release). (Br J Anaesth 2021;127:23)

- Dissociation/**nightmares** if used w/out GABA agent. Higher risk in elderly.
- Falsely **high** BIS
- **Epileptogenic**. May p/w non-convulsive status. **Avoid if seizure risk**.
- **DILI**: ALT>AST rise first, then ALP. ↑ risk w/ chronic EtOH. **Monitor daily LFTs**.

A Generalized Approach to Sedation



Adaptated from Reade and Finfer, NEJM. 2015; 370;444.

Strategies for weaning sedation:

Assess daily for improving resp failure (↓FiO2, PEEP, no NMB).

MGH criteria for extended taper:

Sedation > 7 days + P:F > 200 + transition to PS in 24-48h

- ↓BZDs ~20-25%/day → **phenobarb** or **lorazepam**
- ↓dexmed. ~20-25% q6h → **clonidine** q8-12h or patch
- ↓opioids ~20-25%/day (taper last) → PO opioid (**methadone**)

Pulmonary & Critical Care

Sedation

SEDATION AGENTS (continued)

Opioid Analgesics (as a class)**:** μ-opioid agonists

Analgesia: All are strong analgesics. No amnestic effects. Tolerance & w/d w/ prolonged use (~10-14d) and/or abrupt d/c.
Respiratory: All are **respiratory depressants** and **synergistic with most other sedatives.**
CV: All are **sympatholytic**, but most have limited direct cardiovascular effects → **less ↓BP & less ↓HR vs. propofol.**
- As a class, opioids frequently can cause **constipation/Ileus.**

Hydromorphone Dosing – gtt: 0.5-5mg/hr, bolus: 0.25-1mg q1-q3hr,

Onset/Duration: Intermediate onset (5 min), Intermediate duration ($T_{1/2}$ = 3-4h). **Fewer renal metabolites** vs. morphine/oxy.
- Less adipose accumulation vs. Fentanyl & Morphine → **preferred agent for treatment duration > 24h**.
- Quick onset + short $T_{1/2}$ (vs. morphine) = can be useful for procedural sedation, though less titratable than fentanyl.

Fentanyl Dosing – gtt: 50-250mcg/hr, bolus: 25-100mcg q30-60m,

Onset/Duration: **Fast on** (1 min), Context-sensitive $T_{1/2}$ (↑ lipid solubility)→Bolus $T_{1/2}$: 1-3h vs. gtt $T_{1/2}$: 9-16h. No renal metabolite.
- **Adipose accumulation** → delayed awakening. **Avoid gtt if need frequent neuro checks** (bolus may be useful)
- Rapid onset + short $T_{1/2}$ (if context is short treatment duration) = **useful for procedural sedation.**

Morphine Dosing – gtt: 2-30mg/hr, bolus: 2-4mg q1-q4hr

Cheaper, but **generally less preferred agent**. Fewer ventilator-free & ICU-free days vs. fentanyl (AJRCCM 2021;204:1286)
Onset/Duration: **Slower on** (5-10 min) & **long-acting** ($T_{1/2}$ = 3-5h). Accumulates in renal failure → **avoid if CrCl < 30mL/min**.
Respiratory: Histamine release can cause/exacerbate bronchospasm → **Avoid in reactive airway disease.**
CV: Both longer duration of effect and vasodilatory SEs d/t histamine → **prefer Hydromorphone or Fentanyl if HDUS**.
- Histamine release → **pruritis, urticaria, flushing.**

Benzodiazepines (as a class)**:** GABA agonists

Avoid whenever possible: *BZDs ↑Mortality, ↑time to light sedation & extubation, & ↑delirium*
Analgesia: **None**. || Respiratory: Resp. depression at higher doses. **Synergistic w/ opioids**: be cautious w/ co-administration.
CV: Sympatholytic and synergistic w/ opioids. Be cautious in acutely unstable patients unless prepared to intubate.

Midazolam (Versed): Dosing – gtt: 2-8mg/hr, bolus: 0.5-4.0mg (> 2mg more likely to → apnea), 2mg IV = 5mg IM

Onset/Duration: Bolus = **Fast on** (<1 min) & **Fast off** (bolus lasts 1-2h). Gtt **accumulates in liver/renal failure** and in adipose.
- CYP3A4 substrate: many drug-drug interactions (e.g., fluconazole, macrolides, Flagyl, amiodarone)
- Rapid onset + short $T_{1/2}$ (if context is short treatment duration) = useful for procedural sedation

Lorazepam (Ativan)**:** Dosing – (only) bolus: 0.5-2.0mg, IV=PO, Ativan 1mg ≈ 2mg Midaz ≈ 6mg Diazepam

Onset/Duration: Bolus = **Fast on** (1-2 min) but **longer-acting** (6-8h). Not renally cleared.
- Propylene glycol (solvent) toxicity w/ ↑dose (p/w ↑lactate, ↓BP, arrhythmia, AGMA)
- Longer $T_{1/2}$ = ↑accumulation risk, particularly with shorter bolus intervals

Adjunct Agents: Dopamine Antagonists**: Quetiapine** (50mg q6-12h, max 400mg/d), **Haloperidol** (2.5-5mg IV q4-8h), **Olanzapine** (2.5-5mg). SEs: ↑**QTc** → risk of TdP; ↓gastric motility; extrapyramidal effects, **NMS** (rare, but an emergency) – high fever, "lead pipe" paralysis, hyporeflexia, Rx = dantrolene (takes a long time to prepare).
Neuroleptics: **Valproate (**10-15 mg/kg, max 60mg/kg/day). Many serious SEs: **DILI (boxed warning)**; severe **pancreatitis (boxed warning)**; multiple **cytopenias**: ↓PLTs, aplastic anemia, neutropenia, acquired vWD; SJS/TEN and DRESS.
Barbiturates: **Phenobarbital** (consult pharmacy for dose). Highly effective anti-seizure & ↓ICP; CYP450 inducer (many drug-drug interactions); many serious SEs: CNS depression, respiratory depression, hypotension, bradycardia, SJS/TEN

Pulmonary & Critical Care — Shock

Overview (NEJM 2013;369:1726)

- **Definition**: state of tissue hypoxia due to decreased or dysregulated oxygen delivery or extraction, resulting in end-organ damage
- **Clinical manifestations**: **hypotension** (SBP <90mmHg or ↓SBP >40mmHg from baseline); **end-organ dysfunction**: *oliguria* (UOP <0.5cc/kg/h), **AMS**, metabolic acidosis (± anion gap, **↑lactate**, ↓bicarb 2/2 renal failure); cool & clammy vs. warm & flushed extremities. (Any of these can be **normal—including BP**—in a patient in shock, so a **high index of suspicion** is needed)
- **Initial workup**: focused H&P, ensure **access**, review meds, ECG/CXR, ABG/VBG, CBC/diff, CMP, TnT, lactate, CVO2, monitor UOP

MAP: determined by **CO** (cardiac output) & **SVR** (systemic vascular resistance)

MAP = RAP + CO x SVR → SVR determined by vessel diameter/length and blood viscosity

- (2/3) DBP + (1/3) SBP
- HR x SV → SV determined by preload, afterload, & contractility

Lactic Acidosis (NEJM 2014;371:2309)

Type A: *tissue hypoperfusion*, typical in shock; can be profound iso bowel ischemia, necrosis	**Type B**: *NOT marked tissue hypoperfusion*. Metformin, cancer (e.g. Warburg), EtOH, ↓thiamine, albuterol, D-lactate, mitochond dysfunc., liver dz

Etiologies of Shock

Signs of ↑CO:
- Widened pulse pressure
- Low diastolic BP
- Warm extremities
- Normal cap refill

SHOCK → **↑CO** / **↓CO**

Signs of ↓CO:
- Narrow pulse pressure
- Cold extremities
- Slow cap refill

	Distributive (66%)	Hypovolemic (16%)	Cardiogenic (16%)	Obstructive (2%)
Pathophys.	↓SVR & altered oxygen *extraction*	↓cardiac output → inadequate oxygen *delivery*		
Examples	Sepsis/SIRS, anaphyl., adrenal insuff., liver fail., tox/med, neurogenic (NEJM 2013; 369:840; NEJM 2001;345:588)	**Hemorrhagic**, GI losses, 3rd spacing (pancreatitis) (NEJM 2018;378:370)	**MI, HF,** myocarditis, severe valve disease, **arrhythmias**	Extra-cardiac causes: **PE, tension PTX, tamponade**
Extremities	Warm and dry	Cold and dry	Cold and wet	Cold and dry
CVP/PCWP (Preload)	⇩/normal	⇩⇩ (< 5 mmHg)	⇧⇧(> 7 mmHg)	⇧/normal
CO or CVO_2	⇧/normal (Can be low pre-resuscitation)	⇩ (<70%)	⇩ (<70%)	⇩ (<70%)
SVR (Afterload)	⇩⇩	⇧	⇧	⇧
TTE Findings	Normal chamber size, normal/↑ contractility	Small chambers, normal/↑contractility	Large chambers, poor contractility	Tamponade: pericardial effusion PE/PTX: dilated RV

General Considerations (Any Etiology)

- Vasoactive agents (*Vasopressors*): titrate **MAP >65 mmHg** (cardiogenic MAP >60 mmHg); acidosis = ↓vascular response to pressors
- Ventilatory support: intubate if necessary (concomitant respiratory failure, unable to compensate for metabolic acidosis, marked hemodynamic instability) with pressors available; SpO2 may be unreliable due to peripheral vasoconstriction, use ABG
- PA catheter**:** no mortality/LOS/cost benefit in unselected ICU or CHF pts (Cochrane Rev 2013; JAMA 2005;294:1625; Lancet 2005;366:472)
- Steroids: known adrenal insufficiency / chronic steroids, stress-dose steroids (hydrocortisone 50mg q6h / 100mg q8h x5-7d)
- Bicarbonate: if pH <7.1 or <7.2 w/ severe AKI, can use bicarb amps or bicarb gtt. No mortality benefit except in AKI (Lancet 2018;392:31)
- Refractory Shock: *Consider:* dynamic LVOT obstruction (due ↑inotropy), anaphylaxis, abdominal compartment syndrome, abdominal catastrophe (can be masked by steroids), new obstructive shock (HOCM/PE), and refractory vasodilation
- Rescue therapies: hydroxocobalamin (NO scavenger), methylene blue (reverse NO mediated vasodilation), thiamine, ECMO

Distributive Shock

Septic Shock (see *Sepsis)*; **Anaphylactic Shock** (see *Anaphylaxis*)**; Neurogenic Shock**: Suspect if hypotension is in the context of TBI or SCI. Fluid resuscitate with NS, not LR (slightly hypotonic and will worsen edema in TBI), watch for signs of increased ICP

Hypovolemic Shock

- Access: obtain 3 IVs (16G or less) if possible. Consider Cordis for rapid infusion; TLC, PICC cannot resus. as quickly
- Etiology: poor PO, GI (vomit/stool/fistula), GU (osmotic diuresis/diuretics, hypoaldo, salt wasting), burns, heat stroke, third spacing (pancreatitis, low albumin, trauma), hemorrhage (trauma, surgery, GIB)
- Fluid resuscitation: Crystalloid boluses (LR>NS) unless hemorrhagic shock, then use minimal necessary to bridge to blood availability

Management of Major Bleeding: obtain STAT coags, CBC, fibrinogen, iCa^{2+}. Ensure access. Hold pressure. Correct coagulopathies and consider AC reversal (see *AC Management*). If INR >2, use 4F-PCC (unless ESLD, no INR goal); Plt <50, transfuse plts; fibrinogen <100, use cryoprecipitate. If iCal < 1.10, give IV Ca.

  - If suspect bleed secondary to variceal bleeding, administer octreotide for splanchnic vasoconstriction (*see UGIB*)
  - If surgical/trauma/gyn, consider TXA (1g IV over 10 min → 1g over 8h) or aminocaproic acid (5g IV over 1hr → 1g per hr x 8hr)

- Resus: Transfuse to hemodynamics if bleeding is driving shock. Call for Emergency Blood or Massive Transfusion (*see MTP*)
- Obtain source control: Call surgery/vascular/GI/IR/ pending location of bleeding. Obtain STAT CTA if stable.

Cardiogenic Shock

- Cardiomyopathic: Ionotropic support with dobutamine, 2-5 mcg/kg/minute, diuresis. In MI, revascularization w/ PCI or CABG.
- Arrhythmogenic: *Tachyarrhythmia:* synchronized DCCV, vagal maneuver, adenosine, βB. *Bradyarrhythmia:* atropine, pacing.
- Mechanical: (e.g. due to acute valvular insufficiency). Hemodynamic support, endovascular or surgical intervention.

Obstructive Shock

Relief of obstruction is primary management strategy (see *Tamponade*) (see *PE*)

- PTX: O2, needle decompression or chest tube placement); Avoid mechanical ventilation or BIPPV

Pulmonary & Critical Care — Sepsis

OVERVIEW

- **Definitions**: updated in 2016 by Sepsis Definitions Task Force (Sepsis-3) (JAMA 2016;315:801)
  - **Sepsis**: life-threatening organ dysfunction (↑SOFA score ≥2) from dysregulated host response to infection
  - **Septic shock**: sepsis + (1) pressors to sustain MAP >65 **AND** (2) lactate >2 w/o hypovolemia
- **SIRS may reflect appropriate host response**. SIRS + infectious source not sensitive for sepsis (NEJM 2015;372:1629)

qSOFA
1. RR>22
2. AMS
3. SBP≤100

Sequential Organ Failure Assessment (SOFA) **score**: includes PaO2/FiO2, plts, bili, BP, GCS, Cr/UOP
  - **qSOFA ≥2** can be used to identify pts outside ICU w/ suspected infection likely to have poor outcomes (↑ICU LOS, ↑mortality)
  - Surviving Sepsis Campaign guidelines recommend against qSOFA vs other screening tools as single-screening tool for sepsis and septic shock (Crit Care Med 2021;49:e1063)

PATHOPHYSIOLOGY/CLINICAL MANIFESTATIONS (NEJM 2013;369:840; BMJ 2016;353:i1585)

- Microbial components bind immune cells → ↑inflammatory mediators, PMN migration; if exceeds boundaries of local environment → sepsis (generalized inflammatory response) → tissue ischemia (thrombosis in microcirculation 2/2 altered coag., ↓RBC deformability → ↓O2 extraction), cytopathic injury (mitochondrial dysfunction), impaired endothelial barrier (→ edema) → *organ dysfunction*

Cardiovascular	**Vasodilation** → hypotension; ventricular function may be either hyperdynamic or depressed
Pulmonary	Pulmonary edema, **ARDS**
GI	↑intestinal permeability → ↑bacterial translocation → worsening systemic inflammation
Hepatic	**Cholestasis** ("sepsis-induced cholestasis"), impaired reticuloendothelial function
Renal	**AKI** of multifactorial etiology, including microvascular dysfunction, oxidative stress, global hypoperfusion
Hematologic	Early inflammation, late immunosuppression; procoagulant and anticoagulant disequilibrium: **DIC**, **↓plt**
Endocrine	Altered glycemic control, adrenal dysfunction, sick euthyroid syndrome
Neurologic	Encephalopathy

INITIAL MANAGEMENT (2021 Surviving Sepsis: Crit Care Med 2021;49:e1063)

Sepsis & septic shock are **medical emergencies,** so **early recognition** is critical. Components of initial management include:

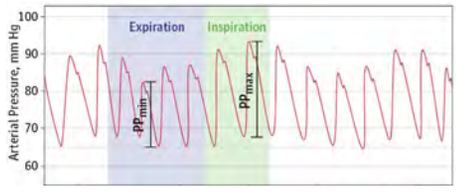
1) Antibiotics: **administer empiric broad spectrum IV antibiotics ideally within one hour of recognition**. **Order STAT**.

- Delay → ↑mortality by 7.6%/h (CCM 2006;34:1589; CCM 2010;38:1045). More rapid abx → ↓mortality (NEJM 2017;376:2235)
- **Abx selection**: guided by infection site, prior micro, community resistance patterns, exposures (SNF, lines, hx abx), host immunity
  - Consider double coverage of PsA if known/suspected PsA infection w/: severe sepsis/septic shock, bacteremia in neutropenic pt, burn pt, or otherwise high incidence of resistance to chosen class (10-15%). Usually β-lactam + (FLQ or aminoglycoside)
  - For ESBL organisms in non-GU infections, carbapenems are preferred to pip-tazo despite micro sensitivity (JAMA 2018;320:984)
  - If there is suspicion of toxic shock syndrome, add **clindamycin or linezolid** for anti-toxin effect (& more staph/strep coverage)
  - If RFs for invasive *Candida* infection (neutropenia, chemotherapy, transplant, indwelling catheters, TPN, recent major surgery [esp. abdominal], prolonged admission/abx), consider empiric antifungals (typically **micafungin**)
- **β-lactam Administration:** After load, extended or continuous infusion of beta-lactams is recommended (Lancet Infect Dis 2018;18:108)
- **De-escalation**: once causative organism identified, Δ to narrowest effective agent, w/ duration individualized to pt/etiology/trajectory
  - Procalcitonin may be useful in guiding cessation (Lancet 2010;375:463; Lancet ID 2016;16:819; CCM 2018;46:684)

2) Resuscitation: **initial resusc. with crystalloid completed w/in 3 hours (~30 mL/kg in most pts, ↑ caution w/heart/renal failure)**

- **Balanced crystalloids** (e.g. LR) with ↓mortality and ↓renal impairment in critically ill adults compared to NS (NEJM 2018;378:829); no mortality benefit to colloids (NEJM 2004;350:2247; JAMA 2013;310:1809; NEJM 2014;370:1412)
- **Targets of resuscitation**: lactate clearance (normalization or >20%/2h) (JAMA 2010;303:739); cap. refill (<3s) (JAMA 2019;321:654)
- After the initial resuscitation effort, further fluid administration should be guided by dynamic measures of fluid responsiveness (see table below). Lack of volume responsiveness → use/increase **vasopressors** instead
- Mortality similar between restrictive vs liberal fluid strategies (NEJM 2022;386:2459; NEJM 2023;388:499)

ASSESSING FLUID RESPONSIVENESS (JAMA 2016;316:1298)

Method	Fluid responsive if:
Pulse pressure variation: validated in mechanically ventilated w/ V_T ≥8cc/kg, not spontaneously triggering ventilator, & in NSR (Crit Care 2014;18:650) Mech ventilation = pos. pressure during inspiration → ↓venous return & RV preload → ↑LV filling/output → PPmax in inspiration, PPmin in expiration **PPV** = (PPmax- PPmin)/PPmean 	PPV ≥13% If on ascending portion of Starling curve, sensitive to Δs in preload. Volume responsive pts will show larger variations in PP or SV during resp cycle
Passive leg raise: raise legs to 45° w/ torso horizontal x1min in any mech. ventilated pt → "autotransfusion" of ~250-350cc; assess Δ in hemodynamics 	↑PP ≥10% (surrogate for ↑SV if no invasive measure of CO)
Fluid challenge: bolus 250-500cc fluids; check CVP before & immediately after, if ↑ ≥2, adequate volume challenge	Improved hemodynamics, UOP, lactate; ↑PP ≥10%

Initial Management Continued

3) Vasopressors: target a mean arterial pressure (MAP) of >65mmHg (NEJM 2014;370:1583) (see *Vasopressors* for full details)
NOTE: permissive hypotension (MAP goal >60) reduces vasopressor use and may be appropriate in select patients (JAMA 2020;323:938).

- Norepinephrine ("levo"): **first choice vasopressor**
- Vasopressin ("vaso"): add when NE at 5-15mcg/min to ↑kidney function. Not titrated, on or off at 0.04U/min (NEJM 2008;358:877)
- Epinephrine ("epi"): recommended when 2nd or 3rd agent is needed; consider trial when NE escalating >25mcg/min
- Phenylephrine ("neo"): recommended primarily when (a) NE is associated with serious arrhythmias, (b) CO is high & BP persistently low, (c) NE + vaso have failed to achieve MAP target at >25mcg/min and pt is ↑tachycardic (d) hypotension a/w AFRVR
- Dopamine: reserved for highly selective patient population with bradycardia and low risk of tachyarrhythmia; a/w ↑risk of arrhythmias/mortality in all-comers (CCM 2012;40:725; NEJM 2010;362:779)
- Methylene blue: used in refractory distributive shock, AE: risk of hemolytic anemia in pt with G6PD deficiency, serotonin syndrome in pts on serotonergic meds)
- Hydroxycobalamin: used in refractory distributive shock, similar mechanism of action as methylene blue
- Angiotensin II: not currently avail at MGH; ATHOS-3 trial (NEJM 2019;377:419)

4) Source Identification and Control

- Cultures: **obtain cultures prior to antimicrobials** (unless will significantly delay administration) as ↑Sn (Annals 2019;171:547). Get at least **2 sets of BCx** with **at least one drawn percutaneously** (see *Bloodstream Infections*)
  - Consider 1,3 beta-D-glucan, galactomannan, and/or cryptococcal Ag if concerned for fungal infection
- Identify conditions that require source control: necrotizing soft tissue infection, abscess, cholangitis, cholecystitis, GI perforation/ischemia, pyelo a/w obstructive renal stone or abscess, empyema, septic arthritis, devices
- **Low threshold to obtain cross-sectional imaging to identify infectious source**

Where to draw blood cultures?
Drawing cultures from vascular access devices can lead to high rates of false positives. **Obtain cultures from vascular access devices only if concerned for CRBSI** (rigors with infusion, erythema/induration around line site); otherwise obtain only peripheral blood cultures

Other Aspects of Management

Corticosteroids

- Rationale: critical illness affects HPA axis, may cause relative "critical illness-related corticosteroid insufficiency" (CIRCI)
- Conflicting evidence regarding mortality benefit of corticosteroids in septic shock: "Annane/French trial" (JAMA 2002;288:862) ↓mortality w/ IV hydrocort 50mg q6h + fludrocort 50mcg/d x7d in pts w/ septic shock, replicated (NEJM 2018;378:809), others showed no Δmortality (NEJM 2008;358:111; JAMA 2016;316:1775; NEJM 2018;378:797). Fludrocortisone + hydrocortisone > hydrocortisone alone (JAMA Intern Med 2023;183:451)
- CAPE COD trial showed mortality benefit for patients hospitalized with severe bacterial CAP (NEJM 2023;388:1931)
- Consider **hydrocort 50mg q6h or 100mg q8h** (≤400mg/d) **+ 0.1 mg fludrocort** in septic shock with ongoing vasopressor requirement (e.g., NE >15-25 mcg/min) (Crit Care Med 2021;49:e1063; Crit Care Med 2024)

AKI

- Timing: **no mortality benefit to early (<12h) vs delayed (>48h) initiation of RRT** in patients with septic shock and severe AKI without urgent indication (NEJM 2018;379:1431; NEJM 2016;375:122; NEJM 2020;383:240)
- Modality: CVVH and HD are largely equivalent for treating AKI, but CVVH minimizes fluid shifts in hemodynamically unstable patients

Metabolic Acidosis/Lactic Acidosis

- Ultimately, **need to correct underlying etiology**. Can temporize with bicarbonate if:
  - Severe acidemia w/ pH <7.1: used as cutoff as evidence in animal/tissue studies of myocardial depression, ↓catecholamine efficacy, arrhythmias, though generally not replicated in human studies & pts w/ DKA can have pH <7 w/o these effects
  - Less severe acidemia (pH <7.2) w/ AKI: BICAR-ICU → $NaHCO_3$ gtt to keep pH >7.3 (≤1L/24h) ↓mortality (Lancet 2018;392:31)
- Bicarbonate administration: **1 amp** = 50mEq/50mL (or 8.4%); or **infusion** of solution of 150mEq (3 amps) in 1L of D5W
  - **Caution**: HCO3 → pCO2 that must be ventilated off, so must have sufficient resp. drive/be intubated. Also → ↓iCa

Transfusions

- Transfusion goal of Hgb 7g/dL unless cardiac ischemia or active hemorrhage (NEJM 2014;371:1381)

Interventions Without Clear Benefit

Vitamin C

- Rationale: Vitamin C is an antioxidant; may also act synergistically with hydrocortisone and thiamine to ↓inflammation
  IV Vitamin C associated w/↑mortality and organ dysfunction compared to placebo in adults w/sepsis (NEJM 2022;386:2387).

Short-Acting Beta Blockers

- Rationale: β-blockade may attenuate harmful effects of sympathetic adrenergic response in septic shock
- Controversy: single RCT ↓mortality in pts w/ septic shock w/ esmolol to keep HR 80-94 (JAMA 2013;310:1683), but control group ↑↑mortality rate (80.5%). Subsequent RCT of landiolol in septic shock did not demonstrate mortality benefit, and point estimate favored standard care group (37.1% vs 28.6%) (JAMA 2023;330:1641)
- Conclusion: need further validation of findings; short-acting beta blockers **not routinely used** in septic shock

Pulmonary & Critical Care

Vasopressors

Category	Name	α	β_1	β_2	D	PVR	SVR	CO
Vasoconstrictors	Phenylephrine	5+	0	0	0	2+	⇧	⇩
	Vasopressin	V_1				±	⇧	-/⇩
Inoconstrictors	Norepinephrine	4+	2+	(+)	0	1+	⇧	⇧
	Dopamine (low)	0	1+	0	2+	±	-/⇧	⇧
	Dopamine (med)	1+	2+	0	2+	±	⇧	⇧
	Dopamine (high)	2+	2+	0	2+	±	⇧	⇧
	Epinephrine	4+	3+	2+	0	1-	-/⇧	⇧
Inodilators	Dobutamine	(+)	3+	2+	0	1-	⇩	⇧
	Milrinone	PDE inhibitor				2-	⇩	⇧
Chronotrope	Isoproterenol	0	3+	3+	0	0	⇩	⇧

α_1: vasoconstriction, ↑duration of heart contraction
α_2: sedation/analgesia, vasoconstriction (if peripheral) vs vasodilation (if central, e.g. clonidine)
β_1: ↑inotropy, ↑chronotropy
β_2: ↑vasodilation
D: renal/splanchnic/coronary/cerebral vasodilation
V_1: vasoconstriction (especially splanchnic)

Pressor Initiation/titration: Start when SBP drops by >30 or MAP <65 WITH end-organ dysfunction despite optimization of volume status. Monitor MAP, UOP, mentation to titrate pressor dose. Responsiveness may decrease over time.
*Subcutaneous medications may ↓effectiveness due to ↑vasoconstriction.

Access: Ideal access is central (CVC, IO)
Temporize w/ peripheral levo (<15 mcg/min) or neo (<150 mcg/min) for <72 hrs. Requires PIVx2, <20G w/ blood return in upper extremity AC or more prox. Check q2h given risk of extravasation (policy). If extravasation, draw back any infusing medication, give **phentolamine** 5-10mg in 10cc NS directly into area of extravasation, apply dry warm compress.

VASOPRESSORS & INOTROPES (Circulation 2008;118:1047)

	Name	Mechanism	Uses	Side effects	Dosing
VASOPRESSORS	Norepinephrine (NE) *Levophed* **"Levo"**	α_1 > β_1 agonist: **↑↑SVR, ↑CO** *Reflex brady from vasodilation can negate ↑HR from chronotropy*	**Septic shock (1st)** **Cardiogenic shock (1st)** **Hypovolemic shock (1st)**	Arrhythmia, ↑LVOT Digital ischemia ↑FSBG	Initial: 2-12mcg/min (0.1-0.15mcg/kg/min) *PIV: <10mcg/min* Max: 35-100mcg/min (0.75mcg/kg/min)
	Phenylephrine *Neosynephrine* **"Neo"**	Pure vasopressor α_1 agonist: **↑↑ SVR**	Septic shock if ↑↑HR from NE *or* ↑CO w/ ↓↓BP *or* 3rd agent needed **AFRVR, HOCM, AS, RV failure**	**Reflex bradycardia** ↓CO, ↑PAP, ↑SVR Digital ischemia	Initial: 50-180mcg/min (0.5-2mcg/kg/min) *PIV: <150mcg/min* Max: 360-1000mcg/min (6mcg/kg/min)
	Vasopressin *Pitressin* **"Vaso"**	V_1 agonist: **↑SVR** V_2 agonist: ↑renal H_2O reabsorption	Septic shock (2nd), add when NE 5-15 mcg/min (↓mortality vs. NE alone) (NEJM 2008;358:877) Anaphylaxis (2nd) Pulmonary HTN/RV failure Hepatorenal syndrome	Coronary ischemia Mesenteric ischemia (especially high dose) ↓Na	Usual: 0.04U/min Consider when NE 5-15 Max: 0.08U/min (only as salvage therapy)
	Epinephrine *Adrenalin* **"Epi"**	Low: β_1 > β_2 > α_1: **↑CO,** neutral **SVR** High: α_1 > β_1 > β_2: **↑CO, ↑SVR**	**ACLS (1st)** **Anaphylaxis (1st)** **Symptomatic bradycardia (2nd)** Septic shock Bronchospasm	↑HR, arrhythmias, ↑LVOT Myocardial ischemia ↑lactate ↑splanchnic SVR ↑FSBG	Low: 1-4mcg/min High: 5-35mcg/min
	Dopamine *Intropin* **"Dopa"**	Low: D_1 > β_1: **↑CO, ↑UOP** Med: β_1 > D_1: **↑CO, ↑SVR** High: α_1 > β_1 > D_1: **↑SVR**	Symptomatic bradycardia Septic shock w/ bradycardia **↑mortality vs. NE** in septic (CCM 2017;45:486) & cardiogenic shock (NEJM 2010;362:779)	Tachyarrhythmia Myocardial ischemia ↓BP (low dose) ↑PCWP, pulm shunt ↑FSBG	Low: 1-2mcg/kg/min Med: 5-10mcg/kg/min High: 10-50mcg/kg/min
	Methylene blue	↓NO and cGMP, ↑smooth muscle tone: **↑SVR**	Refractory vasoplegia in distributive shock Post-cardiopulm bypass Amlodipine overdose Metformin overdose Methemoglobinemia Early MB decreased vasopressor time in septic shock (BMC 2023;110)	Falsely ↓SpO_2 Arrhythmias ↑PVR Rash, hemolysis, serotonin syndrome ⃠⃠⃠ in G6PD Avoid in severe PH (↑PA pressure)	Initial: 1-2mg/kg Max: 5mg/kg
	Angiotensin II	ANG-II agonist: **↑SVR**	Refractory septic shock (*NB*: not available at MGH)	Peripheral ischemia	10-20ng/kg/min; max 40
	Hydroxocobalamin	IV form of Vitamin B12 NO synthase inhibition Modifies H2S (NO and smooth muscle activity)	Tx of vasoplegia refractory to methylene blue treatment (or if methylene blue contraindicated)	Urine discoloration Interference w/ many labs (Clin Biochem 2021;91:31)	Initial: 5g over 15 minutes Max: 30g in 24 hrs
INODILATORS	Dobutamine *Dobutrex* **"Dobuta"**	β_1, β_2 > α_1 agonist: **↑CO, ↓SVR**	Cardiogenic shock Sepsis + ↓LV EF (add to NE/vaso)	**↓BP, ↑HR** Arrhythmias Myocardial ischemia Tachyphylaxis	Initial: 0.5-1mcg/kg/min (2.5 if more severe) Max: 20-40mcg/kg/min
	Milrinone *Primacor*	PDE inhibitor (↑cAMP), ↑inotropy, vasodilation: **↑CO, ↓PVR/SVR**	Cardiogenic shock RV failure (↓PVR, ↓LVEDV)	**Hypotension** Arrhythmias Myocardial ischemia	Initial: 0.125mcg/kg/min Max: 0.75mcg/kg/min
	Isoproterenol *Isuprel*	β_1 = β_2 agonist: **↑HR, ↓SVR**	Symptomatic bradycardia Mg-refractory torsades de pointes	↓BP, ↑HR Arrhythmias Myocardial ischemia Flushing, anxiety	Initial: 2-10mcg/min (can bolus 2-6mcg first) Max: 30mcg/min

Cassandra Fiorino

Pulmonary & Critical Care Toxicology

Tox resident pager 21827 • Poison Control 1-800-222-1222 • MGH Lab Tox Screen Guru: Dr. Jim Flood

	Drug/Toxin	Presenting Symptoms	Diagnostic Workup	Management
Toxidromes	**Anticholinergic** Atropine, Benztropine, Scopolamine, Diphenhydramine	Mydriasis, hyperthermia, ↓sweating, flushing, delirium, urinary retention, ileus, tachycardia, HTN	Hx, EKG, CPK	Supportive, cooling for hyperthermia; charcoal (1g/kg, max 50g) if <1h, BZDs for agitation & seizure, physostigmine if severe (ICU, atropine at bedside; not for TCA ODs)
	Cholinergics Organophosphates, carbamate insecticides, nicotine	"DUMBBELLS": Diaphoresis/Diarrhea, Urination, Miosis/Muscle spasm, Bronchoconstriction/Bronchorrhea, Bradycardia, Emesis, Lacrimation, Lethargy, Salivation/Seizure	ABG, EKG, BMP, CPK, lactate. Can monitor RBC AChE inhibitor if available	100% O_2 (avoid succinylcholine for intubation), atropine (2-5mg, redose to effect q3-5min, no effect on muscular symptoms); pralidoxime (30mg/kg over 30min→8-20mg/kg/h. Only for organophosphate toxicity), benzodiazepines for seizure
	Sympathomimetics Amphetamines, MDMA, cathinones "bath salts"	Agitation, mydriasis, hallucinations, paranoia, tachycardia, HTN, diaphoresis, hyperthermia, piloerection, seizure, vasospasm, ACS	EKG, BMP, lactate, CPK, LFTs, coags	IV BZDs, atypical antipsych, cooling. if refractory agitation, avoid succinylcholine and ketamine
	Neuroleptic Malignant Syndrome (NMS) Dopamine blockade, dopaminergic w/d	AMS, "lead pipe" rigidity, sialorrhea, hyperthermia, dysautonomia, diaphoresis Typically no N/V/D or hyperreflexia	Search for causative agent. CPK (↑↑), CBC (↑WBC), LDH, LFTs, BMP, serum Fe (often ↓); consider brain imaging, LP, EEG	D/c causative agent (restart dopamine if DCd), IVF, cooling blanket, nitroprusside for HTN, BZD for agitation. Dantrolene, bromocriptine, amantadine
	Serotonin Syndrome Antidepressants, Linezolid, Tramadol	AMS, hyperreflexia (LE predominant), hyperthermia, mydriasis, ↑HR, HTN, diarrhea, diaphoresis, clonus, rigidity	Search for causative agent. CBC, CPK, BMP, coags, LFTs, UA, CXR	BZDs for agitation (avoid antipsychotics); supportive care for altered VS (esmolol, nitroprusside for ↑HR & HTN, cooling). If all else fails, consider cyproheptadine
Psychiatric Medications	**Benzodiazepines**	Depressed MS, ataxia, slurred speech, hyporeflexia, ↓RR, coma	Hx, urine tox can give qualitative result	Supportive; avoid flumazenil as it precipitates withdrawal + seizure
	Antipsychotics	Physiologic depression, miosis, anticholinergic effects, extrapyramidal reactions/NMS, tachycardia	CMP, CBC, CPK, LDH, LFTs, serum iron, EKG, EEG	$NaHCO_3$ for QTc prolong.; Mg, isoprot., overdrive pacing if torsades. Avoid class IA, IC, and III antiarrhythmics
	TCAs	Prolonged QRS, arrhythmia, hypotension, anticholinergic toxicity, myoclonus, hyperthermia, AMS, coma, szr	CPK, tox screen, EKG: ↑QRS duration (>100ms, 26% szr risk; >160, 50% risk), terminal R wave >3mm in aVR. Watch for ventricular arrhythmia	$NaHCO_3$ (for the Na) if QRS >100ms or HoTN. BZDs for szr. Salvage: 3% NaCl, lipid emulsion, avoid physostigmine. VA-ECMO for refractory cardiac toxicity and shock.
	Lithium	N/V/D, tremor, hyperreflexia, clonus, ataxia, AMS, szr, AV block, sinus brady, long QT, hyper/hypothyroid, nephrogenic DI if chronic	BUN/Cr, Li levels (nl 0.5-1.5mmol/L), EKG. Toxicity common w/ AKI from NSAIDs, ACEi, diuretics	Frequent neuro checks; IVF (NS preferred), maintain UOP, HD if encephalopathy, renal dysfunction
Pain Medications	**Acetaminophen**	Malaise, vomiting, sweating, RUQ pain, DILI/ALF	See flowcharts in *Consensus Statement*: JAMA 2023;6(8)e2327739 and See *Acute Liver Injury & Failure*	
	Opioids	↓RR & V_T, CNS depression, ↓bowel sounds, miosis	EKG, core temp, FSBG, CPK	IV or intranasal naloxone (0.4-2mg). See *Opioid Use Disorder & Withdrawal*
	Salicylates	Tinnitus, fever, vertigo, N/V/D, ↑RR, pulmonary edema, AMS (can have neuroglycopenia w/ nl FSBG)	ABG (mixed resp alkalosis/met acidosis), BMP, CXR, salicylate level (>30-50mg/dL). Trend levels & ABG q2h	Avoid intubation (if required, hyperventilate to avoid acidemia), IVF, charcoal (1g/kg), glucose (100mL D50), $NaHCO_3$, alkalinize urine to pH 7.5-8, avoid acetazolamide. Consider HD
Cardiac medication	**CCBs**	N/V, HoTN, CHF, ↓HR, AV block, stupor, cardiac arrest, ↑FSBG	Hx, EKG (↓HR, long PR), blood levels (slow, correlate poorly). Extended release more dangerous. High FSBG = poor prognosis	Calcium, pressors, glucagon, HIGH DOSE-insulin (1U/kg bolus, then 0.5-1U/kg/h gtt, adjust to cardiac response) + D10, IVF; consider pacing, atropine, ECMO
	B-Blockers	HoTN, ↓HR, AV block, long QTc (sotalol), CHF, bronchospasm, ↓FSBG, stupor, ↑K, szr (propranolol), miosis	Hx, EKG, blood levels (slow, correlate poorly); propranolol highest mortality	Pressors, calcium, glucagon (5 mg bolus, if no improvement of HR or BP repeat in 10-15 min), high-dose insulin (see CCB), IVF; atropine, pacing, ECMO. HD for atenolol, sotalol
	Digoxin	↓HR, AV block, N/V/abd pain, ↑K, AMS, xanthopsia (yellow-green halo), bidirectional VT, "regularization of AF"	EKG, BMP, UOP, dig level (nl 0.9-2ng/mL; may not be accurate if drawn w/in 6h of last dose, as includes bound Fab fragments)	Digoxin-specific Fab fragments (if K>5.5, severe end-organ dysfxn, or life-threatening arrhythmia), Mg, AVOID hypokalemia
Other	**Cocaine**	Agitation, psychosis, seizure, HTN, ↑HR, vasospasm/MI, arrhythmia, stroke, vasculitis, lung injury, rhabdo	Serum/urine tox (metabolites detectable for 2-5d), EKG, cardiac biomarkers if chest pain, CPK, UA	Hyperthermia treatment (cooling, BZDs), treat chest pain with ASA, CCB, nitrates, (no pure βB). Lido/sodium bicarb for WCT.

Pulmonary & Critical Care — Toxicology

	Drug/Toxin	Presenting Symptoms	Diagnostic Workup	Management
Other Exposure	**Carbon Monoxide**	Minor sx: headache, N/V Major sx: confusion, LOC, seizure, coma, cardiac ischemia, arrhythmias	Hx (house fire, winter w/ space heaters), cyanide & carboxyhemoglobin levels, co-oximetry (SpO2 invalid), AG acidosis, EKG, TnT	100% O_2 ($t_{1/2}$ 250-320 mins→75-90 min); hyperbaric O_2 ($t_{1/2}$ 250-320 mins→30 min); watch for delayed neuropsychiatric sequelae
	Cyanide	HA, nausea, AMS, seizure, coma, shock. Suspect in structural fires, prolonged nitroprusside infusion	Lactate, AGMA, cyanide & carboxyhemoglobin levels	Hydroxocobalamin (5g over 15min, use amyl nitrate if unavailable) & sodium thiosulfate
	Gamma-hydroxy-butarate (GHB)	Agitation, ↓HR, ↓RR, ↓BP, coma (sudden onset/resolution), co-intoxicants common	Not detected on routine tox screen, need 100mL urine & 10-30mL blood for send-out. EKG, r/o other causes, βhCG	Supportive; BZDs for withdrawal. *Note*: OD at low dose if on protease inhibitors
	Synthetic Cannabinoids "Spice" or "K2"	Anxiety, paranoia, sedation, memory impairment, hallucinations, psychosis, szr, tachycardia, HTN, N/V, AKI	Not detected on routine tox screen, can send blood & urine for send-out	Supportive care. BZDs for agitation and szr. Antipsychotics for agitation

(Pharmacotherapy 2015;35:189; Chest 2011;140:795; Crit Care Clin 2012;28:479; Circulation 2023;148:149); see Nephrology for alcohols

Decontamination Therapies

- **Activated Charcoal**
  - Most effective if given when substance is **still in stomach** (usually considered to be **within 1h of ingestion**, but data is lacking)
  - Not useful for: cyanide, lithium, ethanol/methanol, glycols, mineral acids (e.g. sulfuric acid, nitric acid), alkali metals (potassium, magnesium, sodium, including sodium hydroxide [Drano]); iron; ammonia
  - Other therapies not routinely used: whole bowel irrigation (with polyethylene glycol), gastric lavage, Ipecac
- **Dialysis and Acid/Alkaline Diuresis** (consult Nephrology):
  - Dialyzable toxins: methanol, isopropyl alcohol, glycol, acetone, lithium, salicylates, barbituates, INH, atenolol/sotalol, rarely EtOH
    - Acid diuresis (give vitamin C): quinine, PCP; Alkaline diuresis (give $NaHCO_3$): phenobarbital, salicylates, MTX, TCAs

Lung Transplant Overview

- **Lung composite allocation score:** medical urgency & post-lung transplant (LT) survival: use similar factors (e.g., age, Cr, dx, functional status, pCO2, mech ventilation) + cardiac index for post-LT survival, candidate biology: blood type/antibodies & height, patient access (+points for some groups), placement efficacy or proximity/travel (AJT 2022; 22:2971), (OPTN LT policy 2022)
- **Procedure choice:** bilateral LT (BLT) is most common (~80%) d/t better long-term outcomes, but ongoing controversy regarding benefit of BLT vs. single LT (SLT) in COPD and IPF; SLT often not recommended in CF and pHTN (JTD 2018;10:4588)
- **Outcomes**: median survival in adults post-LT 6.7 yrs, some dx have more favorable outcomes (e.g., CF) (JHLT 2019;38:1042)

Lung Transplant Evaluation

As a medicine provider: HCM, tx comorbidities, ⃠ substance use, optimize weight, limit blood product, refer for txp early
Pre-op assessments: Medical: cardiac, pulm, ID, GI, renal, HCM; Surgical/anesthesia; Functional: 6MWT, pulm rehab, nutrition; Psychosocial: SW, psych, financial services, caregiver eval
Contraindications to transplant (JHLT 2021;40(1350))

- Absolute: acute medical instability, significant multiorgan dysfunction (+ untreatable coagulopathy), high risk malignancy, uncontrolled HIV, active TB, hx of non-adherence to medical therapies, active substance use
- Relative: age >70, BMI > 35, EF<40%, active hepatitis, MDRO colonization/ifxn, hx chest surg, severe esophageal dysmotility

Post-Transplant Complications

Early: surgical (post-op hemorrhage), airway (stenosis, necrosis, bronchomalacia), ifxn, 1° graft failure (ischemic-reperfusion injury)
Late Complications (JCS 2022;55:338)

- **Infectious**: typically, donor-derived pathogens in immediate post-op period; bacterial (esp. P. aeruginosa, S. aureus, B. cepacian, E. faecalis), viral (esp. CMV, HHV), fungal (esp. Aspergillus)
- **Malignancy**: esp. dermatologic, SCC #1, post-transplant lymphoproliferative disorder (PTLD)

	Complication	*Diagnostics*	*Treatment*
Immunologic	**Acute-Cellular Rejection (AMR)** (ATM 2020;8:410)	Graded on scale of 0-4 histology, degree of perivascular, interstitial, & air-space mononuclear inflammation	**Initial therapy**: Pulse dose steroids **Refractory**: Repeat steroids, change cyclosporine > tacro, ATG*, sirolimus, ECP*, Cytoxan
	Antibody-Mediated Rejection (AMR) (ATM 2020:8:411)	Clinical diagnosis, detection of donor-specific abs, histology, lung bx C4d staining	Plasmapheresis, IVIG, rituximab, proteasome and complement inhibitors (usually steroid-resistant)
	Chronic Lung Allograft Dysfunction (CLAD): Bronchiolitis Obliterans Syndrome (BOS) & Restrictive Allograft Syndrome (RAS) (JHLT 2019;35:493)	Diagnose based on PFTs – CLAD staged 0-4 depending on FEV1 compared to baseline. BOS is obstructive; RAS is restrictive. RAS mortality > BOS	**BOS**: change tacro > cyclosporine, azithro, TLI*, fundoplication if +GERD, NO steroids **RAS**: experimental -> antifibrotics

*Extracorporeal photopheresis (ECP), total, lymphoid irradiation (TLI), antithymocyte globulin (ATG)

Immunosuppression (ATM 2020;8:409)

- **Induction**: basiliximab (anti IL-2R), alemtuzumab (anti CD52), ATG
  Maintenance: tacrolimus/cyclosporine (CNIs), mycophenalate/AZA (anti-proliferative), sirolimus/everolimus (mTORi), steroid

ACUTE UPPER GI BLEED (AJG 2021;116:5; Annals 2019;171:805; NEJM 2016;374:2367)

- **Definition**: bleeding proximal to ligament of Treitz
- **S/Sx**: hematemesis, melena (on exam: +LR 25; JAMA 2012;307:1072), hematochezia if brisk, BUN/Cr >30 (+LR 7.5; JAMA 2012;307:1072), especially >35 (100% Sp; J Clin Gastro 1990;12:500). Clots in stool make UGIB less likely (+LR 0.05)
- **Risk Stratification and Triage:**
  - High-Risk Features in UGIB: hypotension, tachycardia, coagulopathy (INR > 1.5), Hgb <10, AMS, syncope, age > 65, liver dx, CHF,
  - Risk scores: Glasgow-Blatchford Score and ABC score recommended over AIMS65. Blatchford 0-1 = low risk of rebleeding, consider outpt management) (Annals 2019;171:805; BMJ 2017;356:6432; Gut 2021;70:707;)
  - Triage: May need ICU if BP <90 and HR >100 x2 30min apart; Hct <20/Hgb <7 regardless of vital signs with evidence of active significant bleed in past 12hrs; require >2L IVF or 2u pRBCs to prevent instability/keep Hct >25.

Etiologies (Dig Dis Sci 2018;63:1286)
PUD (~50%; duodenal>gastric): H. pylori, NSAID, EtOH, tobacco, Cameron lesion (in hiatal hernia), Zollinger-Ellison
Esophagitis or gastritis (~30%): GERD, pill, ASA, NSAID, clopidogrel, EtOH, infectious
Varices (~5%): EVB (esophageal) > gastric
Vascular malformation (~5-10%): Dieulafoy's lesion, AVM, GAVE, HHT, XRT, aorto-enteric fistula
Traumatic (~5%): Mallory-Weiss, foreign body, Boerhaave's
Neoplastic (~5%): primary > metastatic
Post-procedural (varies): polypectomy, sphincterotomy
Biliary: hemobilia, hemosuccus pancreaticus

- **Assessment/Management**: Stabilize → Intervene
  - Initial Workup**:** CBC (q2-8hr), CMP, coags, type & screen, orthostatics, abdominal exam, rectal exam to assess stool color.
  - Stabilization: NPO, intubation if high-risk for aspiration (large volume hematemesis, AMS); ensure ≥2 PIV (18G or larger).
    - Resuscitation/Transfusion: IVF (isotonic crystalloid) for hypotension. Do not delay transfusion if active hemorrhage, otherwise transfuse pRBCs for Hgb >7 (NEJM 2013;368:11; Lancet 2017;2:354) or Hgb >8 if CAD (Annals 2019;171:805). Note: Hct drop lags 24-72h from onset of bleeding. For severe/ongoing bleeding (generally after 4u pRBCs), activate massive transfusion protocol (see *Transfusion Medicine*). Avoid overtransfusion, EVs (can ↑ portal pressures and worsen bleeding).
    - Correct coagulopathy: Transfuse for plt >50k. For INR >2 consider PCC (preferred over FFP for lower volume, faster onset). If ESLD, INR inaccurate - avoid FFP (↑volume→↑portal HTN). If uremic, consider ddAVP. No utility to TXA.
    - Consults: GI for EGD and/or colonoscopy, surgery/IR if hemodynamic instability or if endoscopy not preferred
      - **EGD generally within 24hrs**, but no Δ in outcomes if between 0-6hrs vs. 6-24hrs for non-variceal or non-HDUS bleeds (NEJM 2020;382:1299).Barium studies are contraindicated d/t interference with EGD/angiography. NGT placement/lavage is not associated with improved outcomes (ERGH 2017;12:63) and is generally not recommended for diagnosis of UGIB. May be useful for removal of blood/clot to facilitate EGD.
  - Pre-EGD Pharmacotherapy:
    - **IV PPI**: pantoprazole 40mg BID (neutralizing acid stabilizes clots); ↓ high-risk lesions requiring endoscopic therapy but unclear clinical impact pre-EGD (Cochrane Rev. 2010)
    - **IV prokinetics:** erythromycin 250mg 30m prior to EGD ↑gut motility & visualization (Ann Gastroenterol 2016;29:312) Takes time to come from pharmacy. If unable to obtain, substitute 10mg IV metoclopramide
    - For cirrhosis**: IV octreotide** 50 mcg bolus (may repeat bolus in first hour if bleeding uncontrolled) followed by gtt at 50 mcg/hr for 2-5 days. **IV CTX** 1g q24hr x7 days for ppx against bacterial infections and mortality benefit (Gastro 2006;131:1049; APT 2011;34:509). Hold *β*-blockers through day 5.
  - Anticoagulation/Antiplatelet Management: (Gastrointest Endosc 2016;83:3; Am J Gastroenterol 2022;117:542)
    - **Warfarin**: Hold during bleed. For reversal, can consider PCC, but FFP or vit K NOT recommended. Resume after hemostasis (w/ UFH bridge for ~48hrs if indicated; see *Hematology* section). ↓ risk of thrombosis/death in AF if resumed within 7d (Am J Cardiol 2014;113:662).
    - **DOAC**: Hold during bleed. Reversal with idarucizumab, andexanet alfa, or PCC NOT recommended. Resume within 72hrs in high thrombotic risk pts, within 7d for low thrombotic risk pts.
    - **ASA**: Continue during bleed if low-moderate risk, hold if high risk (unless recent PCI/ACS – see below). Resume ASA for 2° prevention after hemostasis endoscopically confirmed (Gastrointest Endosc 2016;83:3) ↑ risk of 30d mortality if not resumed (Annals 2010;152:1); if PUD, add PPI to ↓ risk of re-bleeding.
    - **DAPT for PCI/ACS**: Discuss with cardiologist. Generally if very recent (<30d PCI, <90d ACS), continue both unless life-threatening; if more distant, continue ASA but less risk with holding P2Y12i. Resume within 1-5d pending course
    - Overall, restarting AC/AP sooner → ↓ risk of vascular events, though ↑ risk of bleeding (APT 2019;50:8).
  - Post-EGD Pharmacotherapy/Management: Review GI procedure note for specific diet, PPI, etc. recommendations.
    - For high-risk PUD: **IV pantoprazole** 40mg BID x 72hrs (intermittent dose non-inferior to bolus+gtt [JAMA IM 2014;174:1755])→ ↓re-bleeds and need for repeat EGD. Switch to PO PPI after 72hrs, d/c with BID dosing x 2-8wks. **Treat *H. pylori*** if positive (see GERD and Peptic Ulcer Disease).
    - For variceal bleed: consider **octreotide** x 2-5d, continue **IV CTX** 1g q24hr x5 days. Restart βB on day 5.
    - For angiodysplasia: consider long-term **octreotide** (APT 2012;36:587), **bevacizumab**, or **thalidone** w/ GI help.
    - If re-bleed: consider repeat EGD, angiography, surgical/IR consult. If variceal bleeding, consider balloon tamponade, TIPS, or BRTO.
- **Prognosis:**
  - PUD rebleeding w/o med management: 90% if active bleed, 50% if visible vessel, 30% if clot, 20% if ooze, else <10%.
  - EV bleed: 40-50% resolve spontaneously; 30% mortality → 70% if continued bleeding; 60% risk re-bleeding overall.

ACUTE LOWER GI BLEED (NEJM 2017;376:1054; Gut 2019;68:776)

- **Definition**: distal to ligament of Treitz
- **S/Sx**: hematochezia (maroon or bright red blood, blood clots; *Note:* BRBPR can be seen in brisk UGIB); rarely melena (requires blood spend 14hr in GI tract); BUN/Cr typically <20 w/ normal renal fxn
- **Risk stratification**:
  - Risk scores: ABC score predicts 30d mortality (Gut 2021; 70:707); Oakland score <8 may predict safe discharge (JAMA 2020;3:e209630, Lancet 2017;2:635)
- **Assessment/Management**: See Figure 1 in AJG 2023;118:208 for flow chart.
  - Initial Workup: CBC (q2-12hr depending on severity of bleed), CMP, coags, type & screen.
    - Colonoscopy is the diagnostic test of choice for **hemodynamically stable** LGIB. CT angiography is diagnostic test of choice for **hemodynamically significant** LGIB (shock index HR/SBP >1). (AJG 2023;118:208). CTA low yield for minor or improved bleed. Tagged RBC scan more sensitive than CTA, but rarely used due to poor localization.
    - If hemodynamically unstable, consider UGIB. 10-15% of patients with severe hematochezia will have UGIB (AJG 2010;105:2636). Diagnose with EGD. NG lavage has poor sensitivity and is not routinely used for diagnosis of UGIB (AJG 2023;118:208).
  - Resuscitation
    - Ensure ≥2 PIV (18G or larger). IVF (isotonic crystalloid) for hypotension. Do not delay transfusion if active hemorrhage, otherwise transfuse pRBCs for Hgb >7 (NEJM 2013;368:11; Lancet 2017;2:354) or Hgb >8 if CAD (Annals 2019;171:805; JAMA 2021;325:552). Note: Hct drop lags 24-72h from onset of bleeding. For severe/ongoing bleeding (generally after 4u pRBCs), activate MTP (see *Transfusion Medicine*). Plt goal >30k or >50k if undergoing procedures.
    - Anticoagulation/Antiplatelet Management
      - Most data extrapolated from UGIB, see AC/AP Management section in Upper GI Bleeding
      - Lower GI bleeding data suggests ASA for 1° prevention should be stopped and generally not resumed. ASA for 2° prevention should not be held; if it is, should be resumed soon after bleed resolves (Gastro 2016;151:271).
  - Approach to intervention:
    - **If hemodynamically UNSTABLE**: Consult GI, IR, and consider surgery.
      - GI: Exonerate UGIB first with EGD (10-15% of patients with severe hematochezia)
      - IR angiography: Employed when patients are too hemodynamically unstable for endoscopy (get CTA first).Therapeutic if embolization done, but risk of bowel ischemia and vascular injury.
      - Surgical consult for subtotal colectomy if cannot locate or control bleed.
    - **If hemodynamically STABLE:** Consult GI for discussion of colonoscopy vs flexible sigmoidoscopy.
    - Colonoscopy: Recommended for most patients hospitalized with LGIB, unless bleeding subsided and pt had colo with diverticulosis in last year (AJG 2023;118:208)
      - Timing: Colonoscopy at 24-36hrs may be a safe approach in most stable patients (Gastro 2020;158:1). Remains controversial, studies show delay has no impact vs ↓ identification of stigmata of hemorrhage, ↓ LOS (Gastroenterology 2020;158:168; J Clin Gastroenterol 2019;53:591; Am J Gastroenterol 2005;100:2395).
      - Bowel preparation: No solid food or red liquids for 8 hours prior, use order set "Gastroenterology Bowel Prep"

History	Etiologies (NEJM 2017;376:1054)
Painless	Divertic. (30-65%), angioectasias (5-10%), hemorrhoid (5-20%)
Abd. pain	IBD (3-5%), ischemic colitis (5-20%), perforation
Weight loss	Malignancy (2-15% neoplasm or polyp), IBD (3-5%)
Fever/diarrhea	IBD (3-5%), acute mesenteric ischemia, infectious colitis (2-5%)
AS/ESRD/LVAD	Angioectasias (5-10%); Heyde syndrome
Recent colo.	Post-polypectomy (2-7%)
Constipation	Stercoral ulceration (0-5%)
Abd/pelvic XRT	Radiation proctopathy/colitis (0-2%)
NSAIDs	NSAID-induced colopathy (0-2%)
Liver disease	Colorectal varices (0-3%)
AF	Acute mesenteric ischemia
Prior GI surgery	Anastamotic ulcers
AAA repair	Aortoenteric fistula
Recent SCT/DLI	Graft-vs-host disease
HDUS(↑HR,↓BP)	Brisk UGIB (13%)

UNIDENTIFIED SOURCE AFTER EGD/COLONOSCOPY (ACG: AJG 2015;110:1265)

- **Source**: ~75% small bowel, 25% UGIB/LGIB
- **Small Bowel Causes**: Common: angioectasia (20-30%), IBD (esp. <40), Dieulafoy's lesion, neoplasm, Meckel's diverticulum (esp. <40), polyposis syndrome (esp. <40), NSAID ulcers; Rare: varices, portal hypertensive enteropathy, amyloid, HHT, Kaposi, inherited connective tissue disorders, congenital vascular abnormalities. Consider Heyde syndrome (triad of AS, GI bleeding, and acquired Von Willebrand syndrome).
- **Assessment/Management**: (ASGE 2017;85:22, see Figure 1 for flow chart)
  - Video capsule (VCE): 1st line but CI if strictures (retention). Consider post-placement IV erythromycin 250mg IV to promote passage
  - 2nd look EGD ± push enteroscopy: (prox 60cm jejunum) if recurrent UGI sx; 2nd look colo: if recurrent hematochezia
  - CT enterography: if ⊖VCE or if risk of strictures (IBD, XRT, prior SB surgery, suspected stenosis); CTE>MRE
  - Balloon enteroscopy (single vs double): if strong suspicion of SB lesion and therapy required; often after ⊕VCE
  - If brisk bleed: CTA if stable then angio. If unstable, can intervene with embolization, enteroscopy, or surgery
  - If no source found: iron repletion; consider octreotide, anti-angiogenic tx; replace aortic valve if Heyde & ongoing bleeding

Gastroenterology — Abdominal Pain

Abdominal Pain History and Physical – Key Elements

History: Location, chronicity, quality, radiation, pain Δ w/ eating or BMs, Δ in BMs (caliber, color, diarrhea, constipation), fever, wt. loss, jaundice, medications (NSAID, abx, steroids), surgeries

Exam: Tenderness, distention, rigidity, rebound, guarding, fluid wave, shifting dullness, auscultation, Carnett's sign (AJG 2017;112:760), Castell's sign, McBurney's point, Rovsing's sign, obturator sign, HSM, abdominal veins, caput medusa, DRE

Special populations: immunosuppressed, sexually active, elderly (Am Fam Physician 2006;74:1537)

RED FLAGS of Acute Abdominal Pain

• HDUS, rigidity, guarding, or rebound • "Pain out of proportion" • "Tinkling" or absent bowel sounds • Gross distention + cannot tolerate PO • Bilious emesis, hematemesis, hematochezia

"Can't miss" Dx: vascular infarct, perforation, extra-intestinal hemorrhage, obstruction, ectopic preg

Initial Tests to Consider

BMP, Ca, Mg, CBC w/ diff, LFTs, lipase, lactate, ESR/CRP, UA, b-hCG, troponin, coags, T&S

Infectious studies as indicated. (Gastro 2020;159:320)

Acute Abdominal Pain – Anatomic Approach

Adapted from (Am Fam Physician 2008;77:971)

Right Upper Quadrant

• Liver pathologies (hepatitis, abscess, Budd-Chiari, portal vein thrombus, Fitz-Hugh-Curtis)
• Biliary pathologies (cholelithiasis/biliary colic, cholecystitis, cholangitis, Sphincter of Oddi dysfunction)
• Extra-abdominal: PE, PNA, CHF

Right Lower Quadrant

• Appendicitis • Lymphadenitis • Ileal Crohn's

Diffuse

Obstruction/SBO/LBO, ischemia, AAA, perforation, peritonitis, gastroenteritis, IBD, dietary, SBP, toxin, meds (iron), cancer, ketoacidosis, adrenal insufficiency, celiac, Familial Mediterranean Fever, hereditary angioedema, Acute Intermittent Porphyria

Epigastric

• Pancreatitis
• Gastric pathologies (GERD, PUD, gastritis/gastropathy, functional dyspepsia, gastroparesis)
• Mesenteric ischemia
• Esophagitis
• Extra-abdominal: MI, Aortic dissection

Periumbilical

• Early appendicitis
• PUD
• Bowel obstruction (SBO >LBO)
• Umbilical hernia

Suprapubic

• Cystitis • Prostatitis
• Urinary retention

Left Upper Quadrant

• Splenic pathologies (splenomegaly, abscess, infarction, rupture, trauma)
• Gastritis, PUD
• Sub-diaphragm or abdominal abscess (either side)

Left or Right Lower Quadrants

• Intestinal pathologies (diverticulitis, colitis, constipation, IBD, IBS, volvulus, lymphadenitis)
• Renal pathologies (nephrolithiasis, pyelonephritis)
• Pelvic pathologies (ectopic preg, fibroids, ruptured cyst, endometriosis, torsion, PID, abscess, epididymitis)
• Hernia
• Hematoma

Image Negative Abdominal Pain

Imaging/Testing (ACR Appropriateness Criteria)

• Acute, nonlocalized with fever: CT AP I+
• Suspect bowel obstruction: CT AP I+ over plain film (no need for PO contrast)
• Suspect mesenteric ischemia: CTA AP
• AAA suspected: HDS stable → CTA AP; HDUS→STAT surgery consult
• Epigastric pain, suspected PUD: H. pylori stool antigen, EGD
• Epigastric, suspect pancreatitis: CT AP I+
• RUQ, suspect biliary: RUQUS followed by MRCP w/ clinical suspicion
• RLQ, suspect appendicitis: CT AP I+ vs ultrasound
• Lower quadrant, suspect diverticulitis: CT AP I+
• Lower quadrant/flank, suspect kidney stone: CT AP I-
• Lower quadrant/pelvic, b-hCG+: pelvic and transvaginal US

Metabolic: DKA, Ca, uremia, heavy metals, AI, Acute Intermittent Porphyria
Meds/Toxins: EtOH, opioids/opioid withdrawal, cocaine, anticholinergics, lead/heavy metal
Functional: IBS, abdominal migraine, functional dyspepsia
Episodic: passed kidney stone, sphincter of Oddi dysfunction
Other: acute MI, angioedema, VZV, eosinophilic gastroenteritis, gastritis, polyradiculopathy, abdominal epilepsy

Centrally Mediated Pain Syndrome (CAPS) and Narcotic Bowel Syndrome (NBS) (Gastro 2016;150:1408) Rome IV Criteria

CAPS: Type of functional GI disorder with freq/near continuous pain not related to impaired gut function, structural, or metabolic causes. Instead caused by CNS sensitization and altered pain signals. Multimodal treatment with therapy/stress reduction/meds. Early psychologic, behavioral, or mindfulness referral (such as Benson-Henry Institute at MGH). Trial SSRI (least analgesic), SNRI, or TCA for 4-6 weeks → dose titration → potentially dual therapy. Psychiatry referral for refractory patients.

NBS: Chronic abd. pain treated with acute high-dose or chronic narcotics. Not explained by structural causes/other dx, and pain worsens when ↓ narcotics. Tx: reduce opioid while controlling pain (consider antidepressants and nonpharmacologic therapy). Education key, esp. re: hyperalgesia. Consider inpatient detox. (AJG 2012;107:1426).

Chronic Abdominal Pain – Etiologies

Adapted from Chronic Abdominal Pain (2015)

Visceral	Somatosensory	Functional
Chronic pancreatitis, IBD, mesenteric ischemia, adhesions, cancer, pelvic etiologies	Anterior cutaneous nerve entrapment (PE: Carnett sign), myofascial pain, slipping rib syndrome, radiculopathies, post-herpetic, diabetic neuropathy	Centrally mediated (functional) pain, functional dyspepsia (see section), IBS, narcotic bowel syndrome (NBS)

GASTROESOPHAGEAL REFLUX DISEASE (GERD) (ACG: AJG 2022;117:1 ; AGA: Gastro 2008;135:4)

Signs & Sx: "heartburn" w/ food (i.e. spicy foods, coffee, soda, chocolate, EtOH) or position (reclining), regurgitation, sour taste after awakening, sore throat, dysphagia, globus sensation, chronic cough/throat clearing, hoarseness, asthma exacerbation, chest pain

- Alarm symptoms: dysphagia/odynophagia, wt loss, GIB, IDA, persistent vomiting, anorexia, new onset age ≥60

Ddx: infectious esophagitis, pill esophagitis, eosinophilic esophagitis (EoE), motility disorder, reflux hypersens./functional dyspepsia

Evaluation: No alarm sxs → trial of 8-wk normal dose or short (1-2 wk) high-dose PPI BID (metanalysis: Sn 79% / Sp 45%; NEJM 2022;387:1207). If alarm symptoms or no/incomplete response to PPI → EGD w/ biopsy: look for tissue damage, complications, or malignancy

- If endoscopy ⊖ but persistent symptoms → ambulatory pH monitoring/impedance testing
- If endoscopy ⊖ but persistent symptoms w/ CP and/or dysphagia → assess for motility disorder w/ esophageal manometry

Management (Gastro 2018;154:302):

- Lifestyle Δs: wt loss (goal BMI <25), tobacco cessation, drinking <2 cups of coffee/tea/soda, "prudent" diet (i.e., high intake of fruits, vegetables and whole grains); ≥30 min exercise daily, no eating 2-3 hours before bed (JAMA IM 2021;e207238)
- PPIs > than antacids/H2RAs for sx relief in empiric tx and optimal for erosive esophagitis (Cochrane Rev 2013)
  - Start low-dose PPI (e.g. 20mg omeprazole) 30min before AM meal. Reassess 4-8wk, uptitrate to high-dose (e.g. 40mg omeprazole), then BID if no relief. Assess at 8w if able to d/c.
  - Maintenance PPI: If sx after PPI d/c or if complications (see below). Lowest effective dose. Test for reflux + EGD at 1yr
    Discontinuing PPI: if on PPI >6mo., taper by 50% per wk to prevent rebound hypersecretion.
  - PPI risks**:** *probable association*: ↓Ca, Mg, Fe absorption, AIN, C.diff/other enteric infxns. *Insufficient evidence for* ↑risk of osteoporosis, CKD, or dementia (Gastro 2017;152:706), (Gastro 2020;115:671).
- H2RAs (famotidine 10-20mg BID): can also use nightly PRN w/ PPI, tachyphylaxis common after wks
- Others: PRN antacids, sodium alginate (APT 2013;38:1059; APT 2014;39:595), baclofen (as adjunct)

Severe/Refractory Symptoms: If no relief after 8w on high-dose PPI BID, refer for EGD/impedance testing & consider ddx e.g. functional dyspepsia (symptoms >3mo; Gastro 2020;158:2286), nonerosive reflux disease, reflux hypersensitivity, EoE, rumination, hiatal hernia

- EoE: dysphagia, GERD sx, food impaction; a/w allergic conditions. Dx with >15 Eos per HPF on biopsy. Tx: PPI, topical steroids (Gastro 2020;158:1776), dupilumab (IL4,13 antibody) (JACI 2022;149:AB312)
- Hiatal hernia: Type I (sliding); Type 2-4 (paraesophageal hernias) – refractory GERD; surgery controversial
- Reflux hypersensitivity: dx w/ pH impedance w/ acid exposure time <4% + reflux symptom association (normal manometry)

- Gastric fundoplication may be superior to medical tx for refractory heartburn (NEJM 2019;381:1513)

Complications:

- **Barrett's Esophagus (BE)**: squamous epithelium → intestinal metaplasia (IM). **AdenoCA** risk 0.38% (IM) vs 0.07% (no IM)/yr. Screen w/ EGD in: chronic GERD sx + ≥3 RFs (>50, white, male, central obesity, tobacco hx, FH of BE or adenoCA) (AJD2022;117:559). Mgmt: indefinite PPI. Surveillance EGD interval depends on degree of dysplasia on biopsy (AJG 2022;117:559)
- **Esophageal stricture**: p/w progressive dysphagia to **solids**. Endoscopy w/ biopsy can differentiate stricture from cancer

PEPTIC ULCER DISEASE (PUD) (BMJ 2019;367:l5495; Lancet 2017;390:613)

Signs & Sx: dyspepsia - intermittent gnawing, dull, aching, or "hunger-like" epigastric pain relieved w/ antacids though 70% are asx (often in elderly and NSAID use); *Associated sx*: early satiety, bloating, n/v

Etiology: majority caused by H. pylori or NSAIDs (idiopathic becoming more common). *Others*: meds (bisphosphonates, clopidogrel, sirolimus), ZES, mastocytosis, HSV, CMV, EBV, fungal infxn, post-surgical, XRT, ischemia (cocaine), Crohn's, sarcoid, critical illness

Ddx: other causes of dyspepsia: biliary disease, gastric CA, celiac, chronic pancreatitis, drug-induced, functional dyspepsia

Evaluation: H. pylori testing in all w/ dyspepsia; if >60 → EGD to exclude CA (AJG 2017;112:988)

- **H. pylori testing**: stool Ag or urea breath test (not avail. at MGH) preferred to dx active infection. Testing affected by PPI & abx (↑ false ⊖) but not affected by H2RAs. Serology (IgG) not affected by PPI/abx/bismuth but cannot distinguish active vs. past infection; a ⊖ serology excludes infection if low pre-test probability. Bx w/ urease, histology or cx
- **EGD**: biopsy malignant-appearing & select benign-appearing ulcers; obtain samples for H. pylori testing. Rebleed risk per Forrest classification.

Forrest Class - Description	Re-bleed
Ia - Active arterial bleeding	85%
Ib - Oozing w/o visible vessel	30 %
IIa - Non-bleeding visible vessel	40%
IIb - Adherent clot	25%
IIc - Flat spot	10%
III - Clean ulcer base	3%

Management: PPI (duration depends on etiology); if need to continue ASA, continue w/ PPI (NEJM 2005;352:238; Gastro 2010;138:82). F/u EGD after 8-12w if refractory sx (see below) or most gastric ulcers to exclude malignancy (Gastrointest Endosc 2010;71:663).

Treatment for H. pylori (AJG 2017;112:2)(Gastro 2016;151:51)

- First line = quadruple therapy: PPI BID, bismuth 300mg QID, tetracycline 500mg QID (alternative: doxy 100mg BID), metronidazole 500 QID x 14d. Combo pill (Pylera) available.
- Salvage therapy: Avoid antibiotics used previously. Trial clarithromycin, levofloxacin, or amoxicillin-based regimens (AJG 2017;112:2). Recently approved combined treatment with rifabutin, amoxicillin, and PPI BID for 14d (as salvage therapy) was shown to have no difference in eradication rates but ↑ compliance and ↓ AEs compared to bismuth quad. therapy (J Inf Dis 2023;228:511).
- Confirmation of eradication: confirm for all pts w/ stool Ag, urea breath test, or EGD >4 wks after completion of abx and off PPI for 2w.

Refractory PUD: ulcer that does not heal after 8-12wks adequate tx; 5-10% of ulcers are refractory to PPI tx

- Ensure H. pylori eradicated, NSAIDs & other contributing meds discontinued. Test for ZES w/ fasting serum gastrin (if on PPI, recheck 1 week s/p cessation); secretin stimulation test if non-diagnostic. Search for rare causes.
- Continue PPI x additional 12w and then repeat EGD. Surgical tx: rarely required; resection, vagotomy, partial gastrectomy

Complications and Management: ulcer considered *complicated* if any of the following are present: bleeding: *see Upper GI bleeding*; perforation, or gastric outlet obstruction: pyloric channel/duodenal ulceration → inflammation → fibrosis/scarring; May need endoscopic dilatation or surgical tx if persists despite medical mgmt. If gastric outlet obstruction sxs - exclude malignancy.

Gastroenterology — Functional Dyspepsia

Definition (Rome IV criteria)

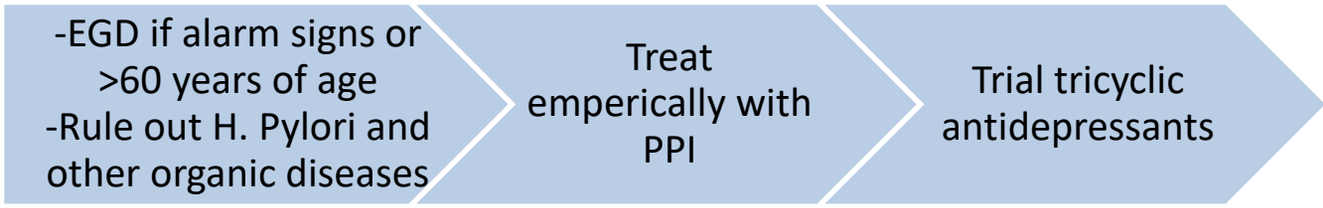
- Functional dyspepsia (Must have one of the following and no evidence of structural disease (endoscopy))
    - Bothersome post-prandial fullness, early satiety, epigastric pain, epigastric burning

Workup (AJG;112:988)

- Should exclude organic causes for dyspepsia including GERD, PUD, biliary type pain, chronic pancreatitis.
- Physical exam may be positive for epigastric tenderness. Assess for Carnett's sign (worse pain with tensing abdominal muscles) to exclude abdominal wall pain.
- Alarm features include: Weight loss, difficulty with swallowing, risk factors for cancer, lab abnormalities (including anemia), which should prompt EGD. In patients >60 years of age, should proceed with endoscopy without alarm signs
- Test for H pylori, and treat if positive prior to considering other management options

Management (AJG;112:988)

- If there are no other causes identified and H Pylori is negative or treated, can trial PPI
- If PPI ineffective in above setting, can trial TCA. The following step could be pro-kinetic therapy but there is low evidence.
- There is also low-quality evidence regarding utilizing psychologic therapies in functional dyspepsia in contrast to IBS


-EGD if alarm signs or >60 years of age
-Rule out H. Pylori and other organic diseases
Treat emperically with PPI
Trial tricyclic antidepressants

Patient communication

- Some patients worry that a functional diagnosis is saying that the issue is in their head. However, it is important to frame that we do not believe that the diagnosis is all in their head. Rather it may be helpful to frame that there are many neuronal connections between the central nervous system (brain) and enteric nervous system (gut), and that they experience real discomfort and pain, but it could be a misinterpretation of signaling. Not unlike some forms of tinnitus. May help with also discussing interventions such as TCA, which works on the connection (neurotransmitters) between neurons.

APPROACH TO PATIENT WITH ACUTE (<1MO.) NAUSEA/VOMITING (Gastro 2001;120:1, AFP 2007;76:1)

1) **Initial assessment**
   a. **Rule out life-threatening causes: bowel obstruction, perforation, mesenteric ischemia, pancreatitis, MI, DKA, ↑ ICP**
   b. **History:** onset, frequency, & severity, hematemesis, feculent vomit. Last BM, LMP
      Triggers: relation to POs, relation to time of day, recent foods/meds, sick contacts, drug use (opioids, marijuana)
      Other symptoms: abd pain (see *Abdominal Pain*), fever, wt loss, diarrhea, melena, heartburn, vertigo, headache, CP, SOB
      PMH: head trauma, prior abd surgery, uncontrolled DM, migraines
   c. **Exam:** dehydration, orthostatics, jaundice, abdominal tenderness, masses, lymphadenopathy, CN exam/nystagmus, gait
2) **Labs to consider:** BMP, LFTs, lipase, B-hCG, UTox, UA, ABG, lactate, cort stim, TSH, Troponin
3) **Studies to consider:** KUB, EKG, CT abdomen (I+/O+), Barium swallow or EGD, Gastric emptying study, CT head
4) **Manage complications:** IVF to correct hypovolemia. Address electrolyte abnormalities (hyperchloremic metabolic alkalosis, HypoK)
5) **Address underlying cause while treating sxs** (see table)
   - Chemo PPX: dex ± lorazepam ± ondansetron ± aprepitant ± olanzapine (NEJM 2016;375:134)
   - Adhesive SBO (prior GI surg, hernias, neoplasms, Crohn's disease): conserv. mgmt x 48h (NGT with suction, NPO) → gastrografin per NGT ↓ surgery by 74% (BJS 2010;97:470)
6) **Practical approach to empiric inpatient nausea treatment** (see table with meds and doses below)**:**
   Normal QTc → Start with ondansetron; add prochlorperazine if persistent. Prolonged QTc → Consider lorazepam. If cannot use benzos, can try dexamethasone, scopolamine, or diphenhydramine. If persistent, further w/u and targeted treatment.
   Non-pharm options: acupuncture, meditation, ginger root, inhaled alcohol (AEM 2018;72:2)

Etiologies (VVOOMMIIITING)		Receptor	Targeted treatment
Vestibular & **V**ertigo	Acute/gait instability; labyrinthitis, BPPV, vestibular neuritis, Meniere's disease	Ach, H_1	Scopolamine, dimenhydrinate, diphenhydramine, meclizine, Dix-Hallpike → Epley maneuver
Obstruction	Adhesions, hernia, volvulus, constipation, gastric outlet obstruction	Multiple	NGT, bowel rest, IVF, surgery consult, serial exams Meds: Prochlorperazine, ondansetron, NO metoclopramide (risk of perf)
Operative	Post-op n/v (risk factors: F > M, nonsmoker, post-op opioids, hx of condition, type of surgery), 1/3 cases	Multiple	Ondansetron, aprepitant, dexamethasone (use 2 in combo as ppx if 3+ RFs), gabapentin
Motility	Gastroparesis (common in uncontrolled DM), autonomic dysfunction, cyclic vomiting syndrome, chronic idiopathic nausea (see *Motility Disorders*)	D_2 (periph)	Low fat & insoluble fiber diet, metoclopramide, erythromycin (tachyphylaxis after 4 wks; motilin agonist), diphenhydramine, cannabis abstinence, TCAs, olanzapine, benzos, SSRI/SNRI
Meds	Antibiotics, AEDs, chemo, opioids, cannabis hyperemesis, anti-arrhythmics	D_2 (central)	Stop offending med if possible, prochlorperazine, haloperidol
Inflammation/ **I**nfection/ **I**schemia	Chemo, XRT, bowel ischemia, gastroenteritis, PUD, hepatitis, pancreatitis, cholecystitis, pyelonephritis	5-HT_3, NK1	Ondansetron, prochlorperazine, dexamethasone, olanzapine & aprepitant (chemo), treat underlying disorder (antibiotics, surgery, etc.)
Toxins	Uremia, ketoacidosis, hypercalcemia, food poisoning, hypo/hyperglycemia	D_2 (central)	Prochlorperazine, haloperidol, treat underlying disorder
Intracranial	Elevated ICP, migraine, meningeal irritation, acute glaucoma	Ach, H_1, 5-HT_3	Dexamethasone (if ↑ICP), treat underlying disorder
Nerves	Anxiety, depression, anticipatory nausea, pain	Multiple	Lorazepam (anticipatory N/V), dexamethasone, pain control
Gums/mouth	Mucositis thrush, oral HSV	Multiple	Treat cause; magic mouthwash

Recep.	Med	Dose	QTc	Other side effects
5HT_3	Ondansetron (Zofran)	4-8 mg PO/IV q8h	↑	**constipation**, HA
	Palonosetron (Aloxi)	0.075-0.25mg IV x1	-	more potent
D_2	Metoclopramide (Reglan)	10-20 mg PO/IV q6-8h	↑	EPS (black box), dystonia (peripheral), promotility agent
	Prochlorperazine (Compazine)	5-10 mg PO/IV/PR q6h	↑	EPS, **sedation**
	Haloperidol (Haldol)	0.5-4 mg PO/IV q6h	↑	EPS, **sedation**
Cortical	Dexamethasone (Decadron)	4-8mg PO q4-6h	-	**psychosis**, CHF, ↑appetite
	Lorazepam (Ativan)	0.5-2 mg PO/IV q6h	-	**delirium**, sedation
NK_1	Aprepitant (Emend)	125mg day 1, 80mg days 2-3	-	CYP3A4 inhib, GI upset
CB_1	Dronabinol (Marinol)	2.5-10 mg q4-6h	-	dysphoria, asthenia, ↑appetite
5HT_{2A}, D_2	Olanzapine (Zyprexa)	5-10mg PO QD	↑	metabolic (wt gain, ↑lipids); ↑ mortality in dementia (black box)
H_1, ACh, D2	Promethazine (Phenergan)	12.5-25 mg PO/IV/PR q4-6h	↑	EPS, **sedation**, tissue injury (black box)
ACh, H_1	Scopolamine	0.3-0.6 mg q24h	-	**delirium**, **sedation**, dry mouth, urinary retention, ileus, blurry vision
	Hyoscyamine	0.125-0.25 mg SL/PO/IV q4h	-	
	Diphenhydramine (Benadryl)	25-50 mg PO/IV q6h	-	

Gastroenterology

Nausea & Vomiting

APPROACH TO CHRONIC (>1MO.) NAUSEA/VOMITING (Gastro 2001;120:1, AFP 2007;76:1, AJG 2018;113:647, Rome IV)

Pathology	Symptoms/Diagnosis	Targeted treatment
Gastroparesis	- Early satiety, bloating, N/V, abdominal pain - Can be related to DM, medication, autoimmune, post-surgical, or idiopathic - Dx with GES showing >10% retention at 4hr and/or >60% retention at 2hr or isotope breath test.	Small particle/low fat diet, hydration, metoclopramide, antiemetics, severe: decompression and jejunal feeding. TCAs and Haldol not recommended.
GERD	- Heartburn, epigastric pain, vomiting, regurgitation - Dx clinically or with pH monitor, EGD	Acid suppression, weight loss, diet/habit modification
Gastric Outlet Obstruction	- Epigastric pain, bloating, early satiety, abd distention, abd pain, weight loss - Can be malignant, inflammatory (related to PUD, pancreatitis, caustic ingestion), infiltrative (Crohn's, TB), or iatrogenic. - Dx with CT, barium swallow, EGD	Supportive care, endoscopic intervention (eg dilation), txt underlying cause. May need NGT decompression
Eosinophilic Gastroenteritis	- Abdominal pain, early satiety, N/V diarrhea, weight loss. Can involve anywhere in GI tract. Likely allergic etiology - Dx with eosinophilic infiltration of stomach on histology	Elimination diet, PO steroids
Cyclic Vomiting Syndrome	Rome IV criteria (must include all): - Stereotypical episodes of vomiting regarding onset (acute) and duration (less than one week) - Three or more discrete episodes in the prior year and two episodes in the past six months, occurring at least one week apart - Absence of vomiting between episodes, but other milder symptoms can be present between cycles	Supportive care (IV fluids + mIVF w/ dextrose, antiemetics), abortive (sumatriptan, aprepitant, Zofran, antihistamine, BZD), prophylactic (TCA, anticonvulsant, CoQ10)
Cannabinoid Hyperemesis Syndrome	Rome IV criteria (must include all): - Stereotypical episodic vomiting resembling cyclic vomiting syndrome in terms of onset, duration, and frequency - Presentation after prolonged excessive cannabis use - Relief of vomiting episodes by sustained cessation of cannabis use	Acute: Supportive (IV fluids, antiemetics, dopamine antagonist, capsaicin cream, Long term: Cannabis cessation
Rumination Syndrome	Rome IV criteria (must include all) - Persistent of recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or mastication and swallowing. (NB: regurgitation is commonly misdiagnosed as vomiting) - Regurgitation is not preceded by retching Dx: Consider pH study/manometry to confirm dx and imaging/EGD to rule out obstruction. History helps distinguish from GERD. Regurgitation typically lacks acidic taste, and sx are refractory to PPI/ less likely nocturnal.	Reassurance, Diaphragmatic breathing (mainstay of treatment, reduces intragastric pressure), baclofen for refractory sx
Pregnancy Associated and Hyperemesis Gravidarum	-Starts at 5-6wks, often peaking at 9wks and subsiding by 20 wks. If n/v starts in latter half of pregnancy, alternative dx should be r/o -HG: ketonuria, weight loss of >5% or vomiting +x3/day and 3kg weight loss -Motherisk-PUQE Score and Rhodes Index tools to determine severity	Supportive: Frequent, small, cold meals with high protein content separated from fluid intake. Ginger and Vitamin B6 +/- doxylamine are first line. If not resolved and no hypovolemia, switch to diphenhydramine. If hypovolemic, call MFM, IVF + thiamine and trial ondansetron if >10wks.

*Also consider non-GI causes such as medications, pregnancy, vestibular, and neurologic disorders

Gastroenterology

Diarrhea

ACUTE DIARRHEA: ≥3 loose stools/d for <14d (ACG: AJG 2016;111:602; IDSA: CID 2017;65:e45; NEJM 2014;370:1532)

- **Evaluation**: small bowel (absorbs ~10L) = watery, large vol., +cramping/bloating; large bowel (absorbs 1L) = freq., small vol., painful, ± fever, blood, mucus. Most acute diarrhea is infectious/viral.
  Exposure hx: travel, abx, hospitalization, food, sick contact, daycare
  "***High Risk***": immunocomp/HIV, IBD, age >70, CAD, pregnant
  "***Severe***": fever > 101.3F, >6 BMs/24hr, hypovolemia, severe pain
- **Workup**: BMP (hypovolemia), C.diff (if risk factors/abx, no retest if confirmed infxn), stool cx (if high risk, severe sx, bloody diarrhea, sx >1wk), stool O&P (3 samples q24h if high suspicion travel, MSM, immunocomp). If bloody, check shigatoxin and fecal leukocytes.
- **Common pathogens**: *See table*. Immunocomp: CMV, *C. diff, Cryptospor., Isospor., Microspor*., MAC, TB, Histopl., Cryptococcus
- **Treatment**: volume & electrolyte repletion. Empiric abx: controversial; consider FQ or azithro if severe sx (see above), high risk, septic, bloody diarrhea, age ≥70, or serious comorbidities. **Avoid abx if suspect STEC** as can ↑ risk of HUS. Probiotics not recommended except for post-abx diarrhea.
- **Anti-diarrheals**: If NO fever/blood/c diff consider loperamide 4 mg x1 then 2mg after BM, max 16 mg/d, diphenoxylate, soluble fiber. If fever/bloody stool can try PeptoBismol 30mL q30min (for 8 doses)
- **Diet:** potatoes, noodles, rice, oats, bananas, soup, broiled veggies

Pathogen	Details
Viral (most cases)	
Norovirus	Outbreaks during winter; n/v prominent
Rotavirus	Daycare-associated
Adenovirus	A/w conjunctivitis + pharyngitis
Bacterial (most severe cases)	
E. coli	Toxigenic = traveler's diarrhea; hemorrhagic, O157:H7 = undercooked meats, a/w Shiga toxin, HUS
Campylobacter	Undercooked/unpasteurized foods, can be a/w reactive arthritis or GBS
Salmonella	Eggs, poultry, milk, often bacteremic
Shigella	Low inoculum, often hematochezia
Vibrio spp.	Shellfish/salt water; RF: cirrhosis
Yersinia	Undercooked pork, "pseudoappendicitis"
C. diff	See *C. diff*
Parasitic	
Giardia	In MA, outdoor streams; watery stool progressing to malabsorptive/greasy
Cryptosporidia	Water-related outbreaks
Cyclospora	Contaminated produce
E. histolytica	Contaminated food/water outside US, a/w liver abscesses

CHRONIC OR PERSISTENT DIARRHEA: Chronic = ≥3 loose stools/d for >4w; Persistent = between 14-30 days

5 types: *secretory, osmotic, functional, malabsorptive, and inflammatory*

Evaluation (Gastro 2017;152:515; CGH 2017;15:182; Gut 2018;67:1380

- Hx: freq., stool vol., tenesmus, abd pain, bloating, postprandial sx, steatorrhea, surgical hx, travel, immunocomp., meds, diet.
- Alarm features: onset >50y, bleeding, nocturnal pain/diarrhea, progressive pain, unexplained fever/weight loss
- Labs: CBC, BMP, LFTs TSH; stool lytes (Na, K, pH), fecal calprotectin (marker of neutrophil activity)/lactoferrin (marker for fecal leukocytes), fecal elastase, fecal fat (24-48h collection), FOBT, *Giardia*, celiac panel (Gastroenterology 2019;157(3):851)
  - Negative fecal calprotectin/lactoferrin rules out IBD; ⊕ FOBT w/ diarrhea suggests chronic infection or IBD (poor sensitivity for colorectal cancer). Other tests to consider: colonoscopy (especially if alarm features or concern for IBD/microscopic colitis), total stool bile acid, *C. diff* (recent antibiotics), *Cryptosporidium/Cyclospora* (travel; exposure to infants in daycares), *Microsporidium* (immunocompromised), KUB (overflow incontinence)
- **Stool osmotic gap for watery diarrhea**: 290 – 2*(stool [Na] + [K]); normal 50-100mOsm/kg

	Watery			Fatty	Inflammatory
	Secretory	*Osmotic*	*Functional*	*Malabsorptive/Maldigestive:*	
Etiologies	Addison's, neuroendocrine tumors, hyperthyroid, medullary CA of thyroid, mastocytosis, **microscopic colitis (lymphocytic or collagenous),** DM autonomic neuropathy, amyloidosis, **bile salt (4-5%)**, lymphoma, villous adenoma	Lactose intolerance, mannitol, sorbitol, magnesium, laxative use, FODMAPs	IBS, functional diarrhea (see *IBS*)	Malabsorption: mesenteric ischemia, mucosal disease (CD, Whipple's), short gut syndrome, SIBO Maldigestion: bile acid malabsorption (ileal disease) or ↓ synthesis, pancreatic exocrine insufficiency	IBD, invasive bacteria/parasite (C. diff, E. histolytica, Yersinia, TB), ulcerating virus (CMV, HSV), colon CA, lymphoma, radiation
Mechanism	Secretagogue, rapid transit, ↓ surface area	Osmotic substance	Multi-factorial	Structural problem, mucosal disease, panc. or bile acid insufficiency	Inflammation interferes w/ function/absorption
Osmotic gap	<50	>125	50-100	Usually >50	Usually <50
Response to fasting	No change	Improves	Variable	Improves	No change
Further Testing	Exclude infxn. +/- colo with bx (esp. if immunosupp). As appropriate: chromogranin, gastrin, somatostatin, calcitonin, 5-HIAA, TSH, ACTH stim, SPEP	Stool pH (<6), H2 breath test, laxative screen	None	Sudan stain, 24hr fecal fat (>20g likely panc dysfxn, 14-20g likely small bowel cause), stool elastase or chymotrypsin, see *Celiac*	Exclude infxn. Calprotectin, fecal leukocytes, colo w/ biopsies
Treatment	Bile salt: cholestyr. 4g QD-QID Microscopic colitis: budesonide, cont. loperamide, no NSAID VIP: somatostatin (octreotide 50-250 ug TID SQ) Other: loperamide 2-4mg QID, diphenoxylate 2.5-5mg QID, tincture of opium	D/c offending agent; dietary review	Fiber (psyllium), Viberzi (+pain), hyoscyamine (antispasmodic), Rifaxamin (+bloating), probiotics, TCA/SSRIs	Pancreatic enzyme replacement therapy (pancrealipase 500-2500 units/kg/meal); If s/p CCY, cholestyramine	Abx vs. immunosuppression (induction vs maintenance tx)

Gastroenterology Constipation, IBS, & Colonic Disorders

CONSTIPATION

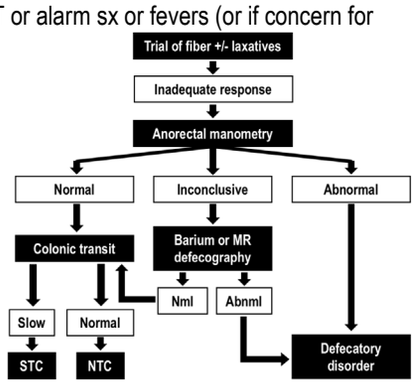
Symptoms: Dissatisfaction with defecation with at least 2 of the following: <3 BM per week, hard stools, straining, sensation of incomplete evacuation, sensation of anorectal blockage/obstruction, or manual facilitation of BM. See Rome IV for exact criteria.

Etiologies:

- **1° constipation**:
  - Slow-transit constipation (STC): sitz-marker study shows delay in colonic transit; associated with bloating & pain
  - Normal-transit constipation (NTC): normal testing, does not meet criteria for IBS-C, but has constipation sx
  - Dyssynergic defecation (e.g. pelvic floor dysfunction): impaired rectal evacuation w/ normal or delayed colonic transit; inadequate rectal propulsive forces or increased resistance to evacuation (e.g. failure to relax or inappropriate contraction)
  - IBS-C: *see below*; recurrent abd. pain or discomfort a/w hard or infrequent stools or relieved by defecation
- **2° constipation**:
  - Lifestyle: low fiber, dehydration, sedentary
  - Medications: analgesics, opioids, anticholinergics (antihistamines, antidepressants, antipsychotics), iron, aluminum (antacids, sucralfate), diuretics, clonidine, amiodarone, CCB, ondansetron, barium
  - CTD: amyloidosis, sarcoidosis
  - Metabolic: ↑Ca, hypothyroid, ↓Mg, ↓K, uremia, heavy metal poisoning, pregnancy
  - Neuro: autonomic neuropathy, DM, Hirschsprung's, multiple sclerosis, anorexia nervosa, spinal cord injury, PD, stroke
  - Obstruction: anal stenosis, colon ca, stricture, rectocele, compression

Diagnosis/Treatment (AGA: Gastro 2013;144:211; Gastro 2013;144:218; JAMA 2016;315:185; AJG 2023;118:936-954)

- History: duration of sx, frequency & consistency of stools, straining, incomplete evacuation, use of manual maneuvers, alarm sx (sudden change in BMs in >50 y/o, blood, weight loss, strong FH of CRC or IBD), **medications**
- Initial workup: DRE (fissures, hemorrhoids, tone), CBC (for anemia); colonoscopy if +FOBT or alarm sx or fevers (or if concern for IBD/CD); other labs not needed unless otherwise clinically warranted
- Further workup (primarily outpatient): see algorithm from AGA guidelines
  - **Anorectal manometry (ARM), balloon expulsion test:** identifies dyssynergia
  - **Barium, MR defecography**: useful when ARM inconsistent with clinical impression, can identify anatomic abnormalities
  - **Colonic transit study**: via radio-opaque makers (Sitz markers) or wireless motility capsule study (less commonly used)
- Management: see medications below
  - **Secondary constipation**: treat underlying cause
  - **STC/NTC**: fiber, laxatives (PEG, stimulant), hydration; add secretory agents if persists; consider transit study on meds or UGI eval if still no improvement
  - **Dyssynergic defecation**: biofeedback/pelvic floor PT; if persists, eval. for STC/NTC; surgery if structural abnormality

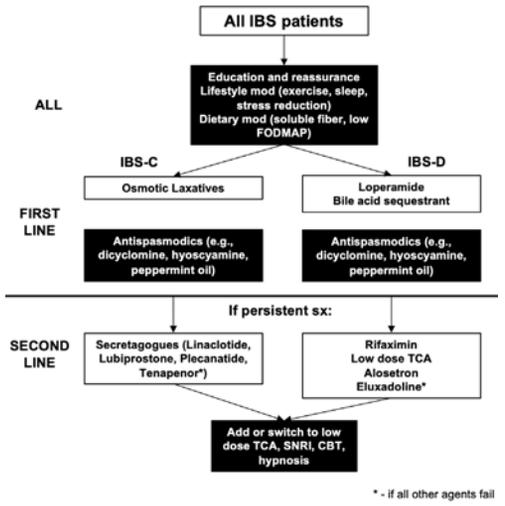


Hospital Constipation Prophylaxis and Bowel Regimens

- Risk factors: >60 yo, prolonged immobility, decreased fluid intake, preexisting constipation, meds (see above)
- Docusate (Colace) lacks evidence in hospitalized pts (J Pain Symp 2000;2:130) & increases cost & pill burden (JAMA Int Med 2016;178:1216); senna 2 tabs QHS > senna + colace (J Pall Med 2008;11:575)
- General ppx for at-risk patients: **senna 2 tabs QHS or BID standing + Miralax 17g daily prn**
- High-risk ppx for patients on opioids: **senna 2 tabs BID standing + Miralax 17g daily standing**
- Stepwise approach: **senna + Miralax → ↑Miralax to 34 g → mag citrate/lactulose → bisacodyl PR → enemas → disimpaction → 1-2 L GoLYTELY** (*Note*: disimpaction can cause vasovagal; all rectal procedures are contraindicated in neutropenia)
  - Types of enemas (stepwise): **tap water → soap suds/mineral oil → milk and molasses (MGH specific) → Fleets**
- Avoid Mg and Phos containing products in renal insufficiency (MOM, Mg citrate, Fleets enema) → can cause nephrocalcinosis

IRRITABLE BOWEL SYNDROME (IBS) (AGA: Gastro 2022;163:118,137)

- Definition (Rome IV Criteria): recurrent abd discomfort ≥ 1x/wk for 3 months a/w 2+ of: (1) related to defecation, (2) Δ in stool frequency, (3) Δ in stool form. No alarm symptoms (sudden change in BMs in >50 y/o, blood, weight loss, FH of CRC or IBD, nocturnal diarrhea, or ↑calprotect/lactoferrin)
- Epidemiology: 10-15% of US adults; younger age pop, ♀ > ♂. Assoc. with fibromyalgia, chronic fatigue syndrome, psych disorders, GERD
- Types: IBS-C (constipation-predominant), IBS-D (diarrhea-predominant), IBS-M (mixed), IBS-U (unclassified), by Bristol Stool Scale
- Initial workup: phys exam as per above; if IBS-D, send calprotec/lactoferrin, Giardia, celiac serologies
- Treatment: all - exercise, diet Δ (low FODMAP), soluble fiber (psyllium preferred, particularly for IBS-M as helps normalize stool)
  - Mild: IBS-C - osmotic lax (e.g. PEG) +/- antispasmodics (dicyclomine, hyoscyamine, peppermint oil); IBS-D – loperamide (45 min before meal, sched), bile acid sequestrant (cholestyramine)
  - Moderate/Severe: IBS-C – secretagogues; IBS-D – rifaximin (2 week trial, can retreat if good resp), TCAs (start at 10mg), alosetron (♀), eluxadoline (↑risk of pancreatitis, contraind. for patients w/o gallbladder, biliary hx, or significant alcohol use)



Gastroenterology — Constipation, IBS, & Colonic Disorders

Colonoscopy Prep

- Adequate preparation = essential. Place pt on clears at noon the day prior to colonoscopy; the prep should start no later than 6PM.
- To prep: 6oz SUPREP (↑ tolerability (AJG 2019;144:305)) + 10oz water → 32oz water over the following hour → repeat both steps in the morning. If stool is not clear, give additional 6oz SUPREP. Contact GI team if not completely see-through to reschedule

Medications for Constipation (Gastro 2013;144:218; JAMA 2016;315:185; ACG: AJG 2023;118:936-954)

Type	Agent	Dose	Notes
Bulk agents	**Fiber:** Psyllium (Metamucil), Methylcellulose (Citrucel)	1 tsp up to TID (for psyllium: up to 30g/d)	Fiber is first-line agent. In some (esp. STC), can ↑ bloating in large amounts. Start low & ↑
Surfactants	**Docusate** (Colace)	50-360mg QD	Less effective than other laxatives; may be inferior to psyllium, not recommended (JHM 2019;14:110)
Stimulants	**Senna**	1-4 tabs QHS or BID	↑ colon secretions, motility. Can cause cramping
	Bisacodyl (Dulcolax)	5-15 mg up to 3x/w up to 4wk	↑ colon motility, can cause cramping. PO QHS or PR AM
Non-absorbed substances (osmotic)	**Polyethylene glycol** Miralax (PEG alone) GoLytely/NuLytely (PEG+salts)	17 g QD; max 34g/d	Modestly more effective/better tolerated (less bloating) than lactulose (Cochrane Rev 2010).
	Lactulose, sorbitol	15-30 ml QD or BID	↑ flatulence/bloating. Less effective than PEG
	Milk of magnesia (MOM)	15-30 mL QD or BID	Benefit of gastric acid neutralization and water retention in stool. Avoid in renal insufficiency
	Magnesium citrate	150-300 mL QD	*Exact mechanism unknown.* Can be used as a lower-volume alternative to PEG bowel prep (2+ bottles + Dulcolax PR). Avoid in renal insufficiency
Enemas	**Tap water, soapsuds mineral oil, Fleets** (sodium phos.)**, milk & molasses**	Varies	All work via lubrication. Soapsuds also stimulates peristalsis. Fleets is hypertonic and also has osmotic effect. Avoid Fleets in elderly or renal insuff. (phos).
Secretagogue	**Lubiprostone** (Amitiza)	24µg BID for STC/NTC; 8µg BID for IBS-C	Binds Cl- channel & increases secretion, ↑ small bowel & colon transit. Most common side-effect is nausea
	Linaclotide (Linzess) **Plecanitide** (Trulance)	145-290µg QD 3g QD	Guanylate cyclase-C agonists; ↑ Cl/HCO3 secretion & colonic transit; Most common side effect is diarrhea
Pro-kinetic drugs	**Prucalopride** (Motegrity)	2mg daily	5-HT4 selective receptor agonist; ↑ cholinergic and noradrenergic neurotransmission to promote motiltiy
Peripheral opioid receptor antagonists	**Methylnaltrexone**, **Naloxegol** (pegylated naloxone), **Alvimopan**	*Methylnaltrexone*: 1 dose SQ QOD PRN - 38-62kg: 8mg - 62-114kg: 12 mg - CrCl <30: 1/2 dose	At MGH, methylnaltrexone approved only if on stable dose of opioids ≥ 2 weeks x3d w/o BM *AND* failed multiple other laxatives. Contraindicated in obstruction, small risk of perforation (AGA guidelines for OIC: Gastro 2019;156:218; Gastro 2019;156:229)

Colonic Disorders

Stercoral Colitis

- Definition: inflammation of colonic wall 2/2 pressure from impacted feces → ↑ intraluminal pressures → ischemic pressure necrosis
- Epidemiology: nursing home residents; bedridden; hypothyroidism; diabetic enteropathy; opioids; clozapine; other constipating meds
- Treatment: fecal disimpaction if no defects in colonic wall on CT; consider CTX/flagyl if septic. Avoid opiates which ↓ motility.

Diverticulosis

- Definition: herniation of colonic mucosa into muscularis propria, where vasa recta penetrate
- Risk factors: low fiber diet ± chronic constipation, ↑BMI, physical inactivity, ↑ age (present in 50% of patients >60yo; common incidental finding), smoking, NSAIDs. ♀ = ♂. Nuts, seeds, popcorn, alcohol, red meat, and fat consumption are **not** associated.
- Location: 90% L-sided (primarily sigmoid) in "Western" populations; 75-85% R-sided in Asia
- Bleeding: **painless** bleeding of *vasa recta* within the diverticuli. 75% are self-limited & resolve with bowel rest. Recurrence is common. Tx if bleeding does not stop: 1) colonoscopy, 2) angio (IR embolization), 3) surgery. See *Lower GI Bleed*
- Diverticulitis develops in 4% of pts with diverticulosis (Clin GI Hep 2013;12:1609).

Diverticulitis

- Definition: infection of diverticuli: micro-perforation secondary to erosion of the diverticular wall by increased intraluminal pressure
  - **Uncomplicated** (75%): abdominal pain (LLQ), fever, leukocytosis, anorexia, Δ in BMs (diarrhea or constipation)
  - **Complicated** (25%): bowel obstruction, abscess, fistula (potentially with bladder, vagina, skin, or peritoneum), or perforation
- Diagnosis: characteristic s/sx & CT A/P (I+,O+) (findings: diverticula, bowel wall >4mm, inflammation w/ pericolic fat ± abscess/fistula)
- Management (AGA: Gastro 2015;149:1944):
  - **Uncomplicated (medical)**: PO abx x7d (cipro/flagyl, bactrim/flagyl, or augmentin), bowel rest. No abx is noninferior to abx if uncomplicated (Clin GI Hep 2021;19:503; Br J Surg. 2019;106:1542)–use selectively (immunocomp., pregnant, comorbidities, sepsis)
  - **Complicated**: IV abx (GNR + anaerobe coverage), bowel rest, and IR/surgical evaluation (peritonitis typically present; evaluation for abscess drainage or colonic resection)
- To prevent recurrence: high fiber diet (Gastro 2015;149:1950), less red meat/refined grain. avoid NSAID, exercise, d/c smoking/alcohol
- Follow-up: consider colonoscopy 6-8w after to evaluate for malignancy; advised in patients with complicated diverticulitis, first episode of diverticulitis, or alarm symptoms; can be deferred if recent colonoscopy (within 1yr) (Gastroenterology 2021; 160(3):906)

Gastroenterology — Esophageal and Upper GI Disorders

		Oropharyngeal Dysphagia	Esophageal Dysphagia
Symptoms		Difficulty **initiating** swallowing; drooling, coughing, aspir.	Difficulty seconds **after** initiation, food **stuck** in esophagus
Etiologies	**Neuro-muscular** (solids + liq.)	Central: tumor, stroke, PD, ALS, MS, polio Peripheral: neuropathy, myasthenia gravis Muscular: polymyositis, muscular dystrophy	1°: achalasia, esophageal motility disorders (e.g. distal esophageal spasm, hypercontractile "Jackhammer" esoph.) 2°: diabetes, scleroderma, CTD, amyloid, Chagas, MG (Chicago classification: Neurogastro Motil 2021)
	Structural (solids > liquids)	Intrinsic: tumor, XRT, trauma/surgery/infection, Zenker's Extrinsic: anterior mediastinal mass, goiter, cervical spondylosis	Intrinsic: tumor, stricture, infection, EoE, rings, webs (e.g., Plummer-Vinson), pills (NSAIDs, doxy, tetracyc., bisphosph) Extrinsic: vascular rings (e.g. dysphagia lusoria), Ao. enlarge., LA compression, mediastinal, substernal thyroid, LAD
Work-up		History: onset & duration, progressive/intermittent, solid/liquid & localization, +/- odynophagia, underlying conditions (e.g., CNS, malig., thyroid, DM, scleroderma), offending meds (pill esophagitis), immunocompromise (Candida, CMV, HSV esophagitis), infectious (Diphtheria, Botulism, Lyme, Syphilis), XRT. Dysphagia in older adults is **not** normal aging PE: appearance (systemic disease or CNS issue), HEENT exam (evidence of LAD, tumor, asymmetry), FOBT Labs (consider): CBC, TFTs, ANA, α-Scl-70, α-centromere, α-RNP, α-Jo, HgbA1C, iron studies, HIV, AChR-Ab	
Diagnostics		1) Bedside swallow, SLP consult, VSS, neuro eval, 2) Modified barium swallow; ENT if c/f mass, voice change, airway involvement. 3) Consider chest/neck CT to dx extrinsic compression	1) EGD may be most useful, though barium swallow is often a good first test (mucosal pathology or structural abnormality) 2) If normal → esoph. manometry to diagnose motility d/o 3) Consider chest/neck CT to dx extrinsic compression
Selected Conditions		**Zenker's diverticulum**: p/w halitosis, regurgitation of food/aspiration, cough. Tx: endoscopic surgery (rigid vs. flexible)	
		Strictures & rings: if lumen <13mm, dysphagia common. Tx: PPI, dilation, intralesional steroid injection, stent	
		Distal esophageal spasm: uncoordinated peristalsis a/w intermittent chest pain & regurgitation; barium swallow: corkscrew (vs. nml). **Hypercontractile esophagus**: similar sx; nml barium swall. Tx (both): PPI, nitrates/CCB/PDEi, TCA	
		Achalasia: progressive dysphagia solids/liquids + regurgitation; barium swallow: bird's beak distal esophagus; manometry: absent distal peristalsis, incomplete LES relaxation; EGD/CT r/o pseudo-achalasia (2/2 CA), Can be a/w Chagas. **Tx:** CCB, nitrates, pneumatic dilation, myotomy, POEM, botox, esophagectomy (AGA: AJG 2020; JAMA 2015)	
		Infectious esophagitis: odynophagia; often immunosuppressed – Candida, HSV, CMV	
		Eosinophilic esophagitis (EoE): dysphagia, refractory GERD sx. EGD w/ stacked rings, strict. Bx: >15 eos/hpf. Tx: PPI, diet Δs (dairy, wheat > soy, eggs, nuts, fish), topical steroids (MDI/neb/liq.); consider dilation (AGA: Gastro 2020;158:1776)	

Gastroparesis (ACG: AJG 2022;117:1197-1220)

Definition: delayed gastric emptying of solid food w/o mechanical obstruction

Sx: **nausea, vomiting of undigested food, early satiety**, postprandial fullness, bloating ± abd pain

Etiologies: **diabetes** (vagus nerve damage 2/2 hyperglycemia), **post-viral**, post-surgical (e.g. vagus nerve injury post-bariatric surgery), systemic disease (thyroid, critical illness, Parkinson's, CTD), **meds** (opiates, CCB, anti-cholinergics), chronically decreased PO

Dx: Gastric emptying tests (hold motility meds, opiates 48h prior). Diagnose with scintigraphy (most common) or wireless motility capsule/C13 breath test. EGD to exclude obstruction.

- Gastric scintigraphy: (radiolabeled egg > liquid) positive if >10% retention at 4hr and/or >60% retention at 2hr.
  - **Indications**: post-prandial n/v, abd pain, early satiety; reflux unresponsive to therapy; patients with DM w/ poor glycemic control; evaluate for rapid gastric emptying; w/u of cyclic vomiting syndrome
  - **Contraindications**: hyperglycemia at time of test > 275 mg/dL, motility agents or opiates within 48-72 hours (JNMT 2008)

Labs: TSH, ANA, A1c, tot protein, alb, CBC/diff

Treatment: Optimize glucose control, small meals w/ low fat & low non-digestible fiber. Prokinetic before meals: (metoclopramide, risk of TD, restrict use <12 wk), erythromycin (tachyphylaxis, give drug holidays after 2wk), D2 agonists (domperidone). Antiemetics (zofran, benadryl). Venting G-tube or pyloromyotomy if refractory. J-tube for nutrition if wt loss. Rec against nortriptyline/haldol.

Celiac Disease (ACG: AJG 2023;118: 59-76; Gastro 2019;156:885; NEJM 2012;367:2419; Vaccines 2020)

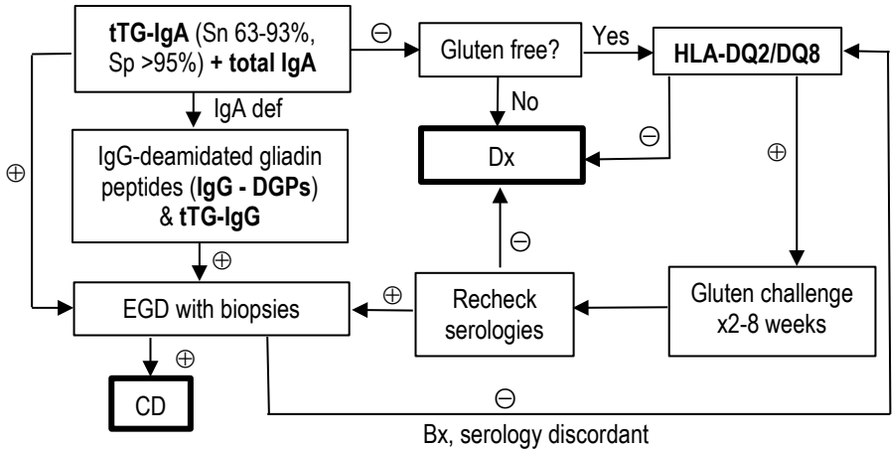
Pathophysiology: abnormal immune response to gluten → diarrhea, wt loss, abd pain, IDA, vit D def, dermatitis herpetiformis

Who: s/sx or laboratory e/o malabsorption i.e., chronic diarrhea with wt loss, steatorrhea, postprandial abdominal pain, bloating; first degree relative; unexplained elevated LFTs; unexplained IDA; diarrhea in T1DM; dermatitis herpetiformis, atrophic glossitis. Adults may have more mild initial presentation than children.

Diagnosis: **see flow diagram**

Biopsy: ↑intraepithelial lymphocytes, crypt elongation/hyperplasia, villous atrophy, Marsh Score AJG 2023;118: 59-76)

Treatment: strict gluten-free diet; IgA anti-TTG titer should normalize over time. Replete vitamin deficiencies (A, D, E, B12), Cu, Zn, carotene, folic acid, Fe +/- thiamine, vit B6, Mg, and selenium. Give HBV booster every 10 yrs.



Gastroenterology — Inflammatory Bowel Disease

Clinical Presentation

Epidemiology: ~1.3% USA prevalence, onset 15-30y, bimodal w/ 2nd peak 50-80y. Genetic predisposition (↑risk: +FamHx, other autoimmune dz; female (Crohn's); ↑incidence in Jewish, white, however increasing dx rate in non-white) + environment (↑risk: Western diet, abx, NSAIDs, sleep deprivation, OCPs; smoking ↑risk for CD & ↓ risk for UC)

Pathophysiology: Inappropriate immune response leading to chronic inflammation of the GI tract. Multifactorial, likely involving genetic susceptibility, immune dysregulation, defective mucosal barriers, and the gut microbiome (NEJM 2020;383:2652)

	Ulcerative Colitis (Lancet 2017;389:1756)	**Crohn's Disease** (Lancet 2017;389:1741)
S/S	*Bloody diarrhea (constipation possible in limited rectal dz)*, lower abd pain (usually LLQ/LUQ), cramps, tenesmus	*Abd pain (usually RLQ), diarrhea (+/- bloody) (constipation w/ strictures)*, n/v, wt loss, perianal fistula/abscess
	Extra-luminal: rheum (seroneg. arthritis, ankylosing spondylitis), cutaneous (erythema nodosum, pyoderma gangrenosum, apthous ulcers), ophthalmic (uveitis, iritis, episcleritis), heme (DVT, AIHA), GU (Ca-Ox / UA stones), pulm (bronchiectasis, ILD), hepatic (PSC)	
Dx	**Continuous** colonic mucosal inflammation spreading proximally from **rectum,** limited to mucosa/submucosa, crypt abscesses, pseudopolyps	**Skip lesions**, strictures, fistulae, **transmural** inflamm., noncaseating **granulomas**, cobblestoning, may involve **any** part of GI tract (including upper)
Complic.	Fulminant colitis, anorectal strictures/dysfxn, perforation	Obstruction (2/2 strictures), abscess, fistula, malabsorption
	↑risk CRC: colo after 8y of active disease, q1-3y w/ random 4-quadrant bx q10cm of colon	
Montreal Classif. Criteria (Gut 2006;55:749)	Extent (proctitis, left sided, extensive pancolitis) Severity (clinical remission, mild, mod, severe)	Age (<16, 17-40, >40) Location (ileal, colonic, ileocolonic, upper GI) Behavior (non-stricturing and non-penetrating, stricturing, penetrating, perianal involvement)

Inpatient Work-up and Management

Hx: stool patterns, bloody BM, nocturnal sx, fever, weight loss, rashes, joint pain, ulcers, vision changes

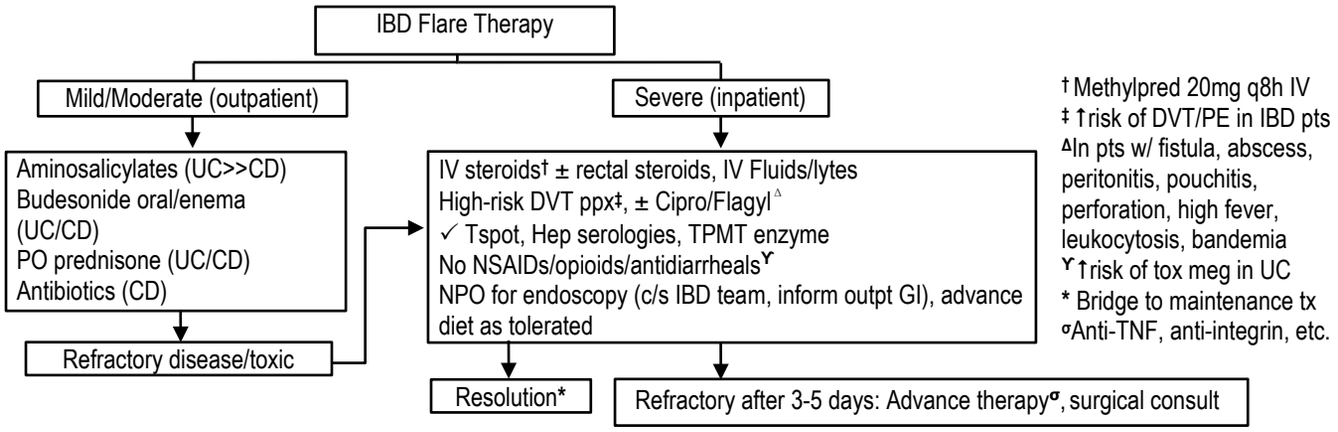
Ddx: infectious colitis, ischemic colitis, celiac disease, lactose intolerance, IBS, diverticular colitis, microscopic colitis, lymphocytic colitis, collagenous colitis, appendicitis, functional abdominal pain

Labs: CBC, BMP, LFTs (↑ALP→?PSC), ESR/CRP, Mg, fecal calprotectin, C. diff, Stool Cx, O&P, Fe/TIBC/B12 (if anemic). *Prior to medication initiation*: Hep serologies and TSpot (immunomodulators), TPMT enzyme (metabolizes AZA toxic metabolites) for AZA. Ensure up to date on vaccines (no live vaccines after starting biologics or immunomodulators).

Imaging: CT A/P if concern for peritonitis/obstruction/mass (abscess). Consider CT/MRI enterography to eval small intestine. Consider pelvic MRI to eval perianal dz

Procedures: Colonoscopy with biopsy (+/- EGD) necessary to confirm dx

Severity	UC (Truelove Witts, Mayo Clinic Score)	CD (CD Activity Index)
Mild	<4 stools (bloody or not), afebrile, nml ESR, Mayo score 3-5	Ambulatory, tolerates PO/no dehydration, no pain/toxicity
Moderate	4-6 BM, bloody BM, low fever, ↑pain, mild anemia, Mayo score 6-10	Failed 1st line tx, low fever, N/V, wt loss, pain, anemia
Severe	>6 BMs, Hb <10.5, fever, HR >90, wt loss, ESR >30, Mayo score 11-12; Pred. of aggressive disease course include <40 yo, disease severity, and early steroid need (Gastro 2020;158:1450)	Failed advanced tx, toxic, abscess, obstruction, peritonitis, cachexia


IBD Flare Therapy
Mild/Moderate (outpatient)
Severe (inpatient)
Aminosalicylates (UC>>CD)
Budesonide oral/enema (UC/CD)
PO prednisone (UC/CD)
Antibiotics (CD)
Refractory disease/toxic
IV steroids† ± rectal steroids, IV Fluids/lytes
High-risk DVT ppx‡, ± Cipro/Flagyl△
✓ Tspot, Hep serologies, TPMT enzyme
No NSAIDs/opioids/antidiarrheals♈
NPO for endoscopy (c/s IBD team, inform outpt GI), advance diet as tolerated
Resolution*
Refractory after 3-5 days: Advance therapy♂, surgical consult
† Methylpred 20mg q8h IV
‡ ↑risk of DVT/PE in IBD pts
△ In pts w/ fistula, abscess, peritonitis, pouchitis, perforation, high fever, leukocytosis, bandemia
♈ ↑risk of tox meg in UC
* Bridge to maintenance tx
♂ Anti-TNF, anti-integrin, etc.

Gastroenterology — Inflammatory Bowel Disease

Step-up therapy: No longer the standard of care for IBD treatment. Treatment instead is guided by risk factors and prognosis. (AGA: Gastro 2021;160:2496).
Poor prognostic factors in CD: Young age at diagnosis, initial extensive bowel involvement, ileal/ileocolonic involvement, perianal/severe rectal disease, deep ulceration, and patients with penetrating or stenosisng disease phenotype (AJG 2018;113:481).
Poor prognistic factors in UC: Young age at diagnosis, extensive colitis, hospitalization for colitis, severe endoscopic disease.
Indications for Surgery: CD: severe stricture, fistulae, abscess, failing medical tx. UC: refractory dz, perforation, toxic megacolon
Management Guidelines: NEJM: NEJM 2021:385:1302

- **CD***:* ACG: AJG 2018;113:481, AGA: Gastro 2021;160:2496
- **UC**: ACG: AJG 2019;114:384, AGA: Gastro 2020;158:1450, Post Proctocolectomy Pouchitis: AGA 2024;166:59

IBD THERAPEUTICS

Class	Drug	Use	Notes & Adverse Effects (AE)
Steroids	Budesonide (PO/PR), Pred (PO), Methylpred (IV)	Induction	**PO budesonide** 1st-line in mild CD, 2nd-line to ASA for mild UC, but can be 1st-line for mod. AE: osteoporosis, infection, AVN, AI, delirium
Aminosalicylates (UC>>CD)	Sulfasalazine Mesalamine (PO: Pentasa, Ascol, Lialda, Apriso. PR: Canasa, Rowasa)	Induction + Maintenance for moderate disease	**Sulfasalazine**: pro-drug with more AEs, also systemic effects **Mesalamine** forms differ in gut penetration: Pentasa (ileum, R>L colon), Ascol (R>L colon), Lialda & Apriso (pancolon), Canasa & Rowasa (distal). AE: HA, fever, rash, diarrhea, pancreatitis, ↓sperm count, AKI
Immunomodulators	Thiopurines Azathioprine (pro-drug) 6-MP	Induction + Maintenance	Typically as combination therapy for induction; can be monotherapy for maintenance. Test Thiopurine methyltransferase (TPMT) prior to use. 6-TGN for monitoring. AE: n/v, hepatitis, BM suppression, malignancy (non-melanoma skin cancer, lymphomas)
	Antimetabolites Methotrexate	Induction + Maintenance	For pts unable to tolerate thiopurines. Typically as combination therapy. Give with folic acid. AE: n/v, hepatotoxicity, BM suppression, lung injury
	Calceneurin Inhibitors Cyclosporine	Induction *only for severe UC*	C/i in s/o toxic megacolon. Labs: troughs (q2-3d) Cr, Mg, lipids, LFTs AE: renal injury,↑K, infxn, neurotox/seizures (esp. if ↓Mg or cholesterol)
Biologics	Anti-TNF Infliximab (Remicade) (IV/SC) Adalimumab (Humira) (SQ) Certolizumab (Cimzia)-CD Golimumab (Simponi)- UC	Induction + Maintenance for mod-severe	**Infliximab** for induction in pts naïve to biologics. Contraindicated if toxic megacolon, pyogenic infxns. Typically in combination with immunomodulator. Preferred agent with concomitant IBD-associated arthritis. **If flare during maintenance**: measure trough (24hrs prior to dose) and antidrug Ab. If non-responsive despite adequate levels -> another class. AE: infxn, TB/HBV reactiv., malignancy
	Anti-Integrins Vedolizumab (Entyvio) (IV/SC) (NEJM 2013;369:699; NEJM 2013;369:711) Natalizumab (Tysabri)	Induction + Maintenance for mod-severe	Induction in pts naïve to biologics. VARSITY (NEJM 2019;381:1215): in mod-severe UC, achieved ↑clinical remission at 52wks vs. Humira, but w/ greater steroid use. AE: infusion reactions, nasopharyngitis ACG recommends against natalizumab due to risk for JC-virus associated PML, can consider if pt adheres to JC virus monitoring
	IL-12/23 Uztekinumab (Stelara) (NEJM 2019;381:1201) Risankizumab (Skyrizi, IL-23 only) (Lancet 2022;399:2031)	Induction + Maintenance	Ustekinumab shown to have no differences in outcomes compared to adalimumab in Crohn's patients (Lancet 2022;399:2200). Sometimes preferred for less frequent ~q8week dosing. AE: infection, HA, nasopharyngitis, nausea, abdominal pain, arthralgias
Small Molecules (Oral)	JAK inhibitors Tofacitinib (Xeljanz) (NEJM 2017;376:1723) Upadacitinib (Lancet 2022;399:2113)	Induction + Maintenance	PO, Consider if previously failed anti-TNFs AE: infection, herpes zoster, HA, nasopharyngitis, arthralgias, CPK elevation, acne
	Sphingosine-1-phosphate receptor Ozanimod Etradimod (Velsipity)	Induction + remission *moderate to severe UC*	Prior to initiation: CBC, LFTs, EKG. Vaccinate for shingles. Ohthalmic exam (uveitis, macular edema). Need sleep study if at risk for OSA. AE: anemia, nasopharyngitis

Diet: Medeterranian Diet for all with IBD. UC: ↓red meat. CD: ↓saturated fats, ↑fruits & veg (Clin Gastro Hep 2020;18:1381)

ILEUS AND SMALL BOWEL OBSTRUCTION (J Trauma Acute Care Surg. 2012;73:S362; J Trauma Acute Care Surg. 2015;79:661)

	Ileus	Small Bowel Obstruction
Definition	Slow gut motility without obstruction	Obstruction of intestinal flow, can be partial or complete
Risk Factors	Intra-abdominal surgery, peritonitis, sepsis, ischemia, meds (opioids, anti-cholinergics); worsened by ↓K	Prior surgery (adhesions), hernia, inflammation (e.g. IBD), malignancy, radiation, foreign body ingestion, gallstones
Signs/ Symptoms	N/V, **mild diffuse pain**, obstipation (↓BMs and ↓flatus), bloating/gassiness, abd distention, tympany to percussion, **↓BS**, no peritoneal signs	N/V (may be **bilious/feculent**), **severe cramping pain**, obstipation, abd distention, tympany to percussion, **high pitched or absent BS**, dehydration, **± peritoneal signs**
Studies	KUB or CT: dilated bowel loops, **air in colon**, **no transition point**, no peritoneal free air	KUB (less useful): decompressed colon, air-fluid levels CT w/ PO + IV contrast: **transition point**, **decompressed colon**, ± peritoneal free air, ischemic signs, closed loop obstruction
Treatment	Bowel rest, decompression via NGT if mod/severe sx, avoid opioids, replete lytes (goal nl), methylnaltrexone if hx opioid use, parenteral nutrition if extended NPO period, treat underlying etiology	Initial mgmt.: Bowel rest, decompression via NGT for N/V and distension, IVF, replete lytes. Broad spectrum abx if c/f ischemia/necrosis or bowel perf Nonsurgical mgmt.: Gastrografin challenge for adhesive SBO only. Draws fluid into the bowel, decreasing wall edema and stimulating peristalsis. Contraindicated in pregnancy, bowel ischemia/necrosis/perf, abdominal surgery w/i 6 weeks Indications for surgery: **any suspicion of ischemia/necrosis or perf**, closed loop obstruction (volvulus), hernia, intussusception, tumor, foreign body, gallstone, SBO persists after 3-5 days

Acute colonic pseudo-obstruction (Ogilvie's): typically elderly, hospitalized pts. A/w severe illness, systemic dz (thyroid, DM, renal or liver failure), neuro (spinal cord compression/trauma, PD, MS), meds (opiates, CCB, anticholinergics). Dx: CTAP + rectal contrast (C.I. if peritonitis) Tx: conservative (NPO, IVF, NGT/rectal tube), neostigmine if cecal diam. >12 or if fail conservative tx. Colonic decompression if fails. (ASGE: Gastro Endosc 2020;91:228)

Sigmoid volvulus: associated with long redundant colon, constipation (may cause sigmoid dilation and prolongation), colonic dysmotility. Insidious abdominal pain, constipation, abdominal distention, nausea. Dx: "Bent inner tube" on KUB, confirmed with CTAP
Tx: Alarm signs (perforation or peritonitis): immediate surgical management (detorsion may cause reperfusion injury). No alarm signs: endoscopic detorsion followed by semi-urgent surgery (allows for complete bowel prep prior to surgery) (World J Emerg Surg 2023;18:34)

INTESTINAL ISCHEMIA (ACG: AJG 2015;110:18; NEJM 2016;374:959)

	Colonic Ischemia	Acute Mesenteric Ischemia	Chronic Mesenteric Ischemia
Chief Concern	- **Cramping pain** (mostly LLQ) → mild/mod **hematochezia** - Uncommon: gangrenous bowel or fulminant colitis	- Arterial: **sudden, pain out of proportion to exam** - Venous: often insidious onset, waxing/waning abd distention, **N/V**, diarrhea ± occult blood	- **Recurrent, post-prandial pain ("intestinal angina")**; dull, crampy, starts 10-30m after PO, lasts 1-3h - N/V, early satiety, BM Δs - Wt loss, **fear of eating**
Etiology & Risk Factors	**Non-occlusive** (95%): - Watershed areas (splenic flexure, rectosigmoid) most susceptible; 25% R-sided - Risk factors: cardiopulmonary bypass, MI, HD, aortic surgery, dehydration, extreme exercise - Vessels: SMA, IMA - Prognosis: 85% spontaneously resolve in 2w, 5% recurrence	**SMA occlusion** (~75%): embolic (40-50%): AF/endocarditis/aortic plaque, thrombotic (20-35%): underlying ASCVD, dissection/inflammation (<5%) **Non-occlusive** (5-15%): hypoperfusion or vasospasm after CV event/surgery, cocaine, vasculitis **Mesenteric vein thrombosis** (5-15%): trauma, surgery, thrombophilia, local inflammation (pancreatitis, diverticulitis, biliary infxn), stasis due to cirrhosis/portal HTN, malignancy Prognosis: mortality 50%, but can be 70-90% if delay in diagnosis leads to intestinal gangrene	- Progressive atherosclerotic narrowing at origins of vessels - Risk Factors: tobacco, HTN, DM, HLD (ASCVD RFs), >60 yo, female, dissection, vasculitis, fibromuscular dysplasia, radiation - Vessels: SMA, IMA, celiac artery - If pain is constant, consider acute thrombosis
Dx	**Labs**: ↑lactate, WBC, LDH, CK, & amylase if advanced. Stool guaiac ⊕ in ~50%. Stool Cx, O+P, C. diff **Imaging**: CT A/P (I+/O+): wall thickening, edema, thumbprinting, pneumatosis, **no vessel occlusion** **Colonoscopy** (to assess extent): petechial blood, pale mucosa, segmental edema/ulceration	**Labs**: most abnormalities arise after progression to necrosis. ↓pH, ↑lactate, AGMA (in 50%), WBC >15K (75%), stool guaiac ⊕ in ~50% **Imaging**: KUB: Ileus, colonic dilatation, pneumatosis. CT A/P (ideally CTA; no oral contrast): wall thickening, pericolonic fat stranding, pneumatosis, arterial occlusion, portomesenteric venous gas. Angiography: if CTA non-diagnostic but high suspicion, or if vasculitis affecting small-medium size vessels; potentially therapeutic with stent/tPA	**Imaging**: - CTA: ⊕ if stenosis of ≥ 2/3 major vessels (celiac, SMA, IMA). 91% with 2 vessels, 55% with all 3 vessels - Doppler U/S to measure mesenteric blood flow and r/o median arcuate ligament syndrome - Gastric tonometry exercise testing - Angiography (see left)
Tx	- Bowel rest, IVF, d/c vasoconstrictive meds - GNR/anaerobic abx if ≥ mod sxs (per society recs) - If suspicion for necrosis, gangrene, or perf, call surgery - If atherosclerosis on imaging, treat with lipid lowering agent	**Occlusive disease**: NGT/NPO, IVF/blood product - Broad-spectrum **abx** - Anticoagulation (**heparin** +/- tPA) if not bleeding for occlusive dx - If infarction/peritonitis/perforation → **surgery** - Thrombectomy/embolectomy vs. intra-arterial vasodilators (IV papaverine) vs. thrombolysis **Non-occlusive**: treat underlying cause (statins etc.) **Mesenteric vein thrombosis**: anticoag x3-6m	- Surgical revascularization: open vs. endovascular or angioplasty +/- stenting, Peri-op mortality 0-16%; no role for prophylactic intervention if asymptomatic - Restenosis common (7% open revasc; 34% endovascular) - TPN for nutrition support - AC if acute-on-chronic ischemia

Celiac artery compression syndrome: chronic, recurrent abdominal pain related to compression of the celiac artery by the median arcuate ligament. Abdominal pain, weight loss +/- nausea, diarrhea. Exam often normal but epigastric bruit may be heard
Dx: arteriography, duplex ultrasound, gastric tonometry, ganglion nerve block Tx: celiac artery decompression (MIS or open) (Cardiovasc Diagn Ther 2021;11:1172)

Gastroenterology — Nutrition & Feeding

General Approach (ACG: AJG 2016;111:315)

1) Assess nutritional status (Clin Nutr ESPEN 2018;26:13)
   - **Hx/Exam**: dietary intake/tolerance, n/v/d, muscle/fat wasting, **weight loss**, functional capacity (grip strength, ADLs). **Screen** for food insecurity (Hunger Vital Sign)
   - **Weight loss as indicator of malnutrition**: >2% in 1 wk, >5% in 1 month, >7.5% in 3 months, >10% in 6 months, >20% in 1yr
   - **Labs:** INR prolongation may indicate malnutrition. Consider vitamin levels if history/exam is suggestive. Albumin can be a helpful marker (may be confounded by sepsis). **Avoid** using pre-albumin, transferrin, retinol binding protein as indicators of nutrition.
   - **24-hr calorie count; nutrition consult** if c/f malnutrition (**screen** with NRS-2002 or NUTRIC Score in hospitalized pts)
2) Determine dietary route (oral > enteral [EN] > parenteral [PN]):
   - **Oral**: assess aspiration risk, dysphagia, odynophagia. Consider SLP c/s for dietary modifications (e.g. pureed, thick liquids etc.)
   - **Enteral (EN)**: NGT if pt unable to tolerate oral diet safely or meet caloric needs through oral diet alone, may need enteral nutrition. **Measuring gastric residuals not recommended** (NEJM 2014;370:1227). In critically ill pts, consider Tylenol absorption test to assess enteral nutrient/med absorption. Place tube post-pyloric (JG/PEG-J) if gastroparesis, gastric outlet obstruction, severe vomiting, or high aspiration risk. Consider PEG if head/neck cancer, dysphagia, neurodegenerative disease, prolonged recovery.
   - **Parenteral**: TPN (central access) or PPN (peripheral). Used when GI tract non-functional or no reliable enteral access anticipated.
3) Initiate diet: early EN initiated within 24-48 hours of admission, advance to goal within 48-72 hours (as tolerated, 3-4 days if refeeding risk). Nutrition/TPN consult for specifics. Watch for refeeding (see below).

Artificial Nutrition

Supplements (order "Adult/Pediatric Nutrition Supplements"): Ensure Plus (standard), Ensure Clear (low fat), Mighty Shake (standard, has lactose), Magic Cup (pudding, dysphagia), Glucerna Shake (DM), Nepro (CKD), Beneprotein (protein powder), Prosource Protein (liquid)

TUBE FEED FORMULAS

Indication	Formula
Normal absorptive capacity	**Osmolite 1.0**
Long-term TF Prevent constipation (high fiber)	**Jevity 1.5**
Wound healing (high protein) ICU patients (on propofol)	**Promote**
IBD, pancreatitis post-abdominal surgery	**Vital** (semi-elemental)
Respiratory failure/ARDS Volume overload (high protein)	**Osmolite 1.5**
Renal or liver failure (low Na/K/phos)	**Nepro**
Wound healing	**Beneprotein/ProSource Liq Protein** (modular protein)
Max fluid restriction	**TwoCal HN** (normal protein, no fiber)
Diabetes	**Glucerna**

TPN: "Nutrition Support Team" in PPD (p22445)
Consider if ≥7d w/o enteral nutrition. Need central access w/ clean dedicated lumen (PICC Preferred). Order by 1PM to start same day. Page about new orders if close to 1 PM.

- Monitor for complications of TPN (if applicable):
  - **Metabolic effects**: hyperglycemia (2x > enteral), serum electrolyte alterations, refeeding syndrome (see below), Wernicke's encephalopathy, hepatic dysfunction, biliary sludge/gallstones. Small amt of insulin included but can be adjusted if needed
  - **Monitor** BMP, Mg, Phos, LFTs, and TGs
  - **Bloodstream infection**: increased risk of infection (**fungal** and bacterial)
- If no central access, **Clinimix** (amino acid solution in dextrose, no fats) can be given as PPN
- **To stop TPN,** coordinate careful transition to EN w/ nutrition; stop when EN provides >60% energy needs (AJG 2016;111:315)

Refeeding Syndrome

Electrolyte/fluid shifts caused by initiation of nutrition in severely malnourished patient (d/t insulin surge and increased Na/K pump activity), can be fatal; most likely to occur within 72h of starting nutritional therapy (Nutrition 2018;47:13; Front Gastro 2019;11:404)

- Risk factors: minimal/no intake for 5 (minor) to 10 (major) days, significant wt loss, age, excessive alcohol use, malnutrition 2/2 chronic dz/malabsorptive conditions, anorexia nervosa, persistent n/v/d, low initial lytes (J Clin Med 2019;8:2202)
- Characteristics: **early**: ↓Phos, ↓K, ↓Mg, vitamin deficiency (thiamine); **late**: cardiac damage (CHF), respiratory failure (volume overload); **other s/s**: AMS, n/v, diarrhea, tremors, paresthesia
- Prevention and management: close lab monitoring (**at least BID when concerned**) w/ aggressive repletion of electrolytes (Phos, K, Mg, Ca; IV preferred) for first 3 days & administer thiamine **before** refeeding regardless of level, slow/hypocaloric initial feeding, consider fluid/sodium restriction, cardiac monitoring in high-risk patients. Stop feeding if electrolyte abnormalities persist.

Special Considerations

- **IBD flares, pancreatitis**: early enteral feeding (ideally within 24-72 hrs of admission)
- **Critical care**: EN should start within 48 hrs of ICU stay (superior to TPN if GI tract functional); contraindications include high dose pressors/unstable (risk of bowel ischemia, hold off until patient more stable) or significant GI pathology (e.g. GI bleed or obstruction) for which patient should be NPO (Clin Nutr ESPEN 2019;38:48)
- **Dementia**: avoid dietary restrictions, use nutritional supplements as needed; guidelines recommend against TFs in advanced dementia (a/w higher mortality), lack of evidence to support appetite stimulants (Nutr Clin Pract. 2014;29:829; Clin Nutr 2015;34:1052)

Tips for Ordering Inpatient Diets

- **Diabetes: Consistent carbohydrate** (must add carb gram restriction within order)
- **Cardiac: no added salt** (4g) vs **2g Na** (renal/liver/cardiac). Consider fluid restriction (usually 2L) for HF/SIADH/cirrhosis
- **GI: low fat (GI)** for gallbladder dz/fat malabsorption/pancreatitis, **red dye restricted** for pre-EGD/colo
- **Renal: low K** (2 g), **low protein** in some CKD (NOT dialysis), **low phos** for ESRD
- **Onc: Neutropenic/BMT** (no garnishes), **PET scan** is carbohydrate restricted

Gastroenterology — Pancreatitis and Pancreatic Mass

ETIOLOGY (NEJM 2014;317:1983)

- **Gallstones/sludge** (40-75%): #1 in female sex
- **Alcohol** (30%): #1 in male sex
- **Hypertriglyceridemia** (10%): #3; suspect if TG>1000
- **Anatomic**: ampullary diverticula/stenosis, duodenal stricture, tumor, divisum, parasites, foreign body
- **Post-ERCP**: 4.5% of ECRP; rectal NSAIDs ↓risk (Endoscopy 2020; Endosc Int Open 2019;7:477)
- **Autoimmune**: ↑IgG4, +ANA (Am J Gastro 2018;113:1301)
- **Acute hypercalcemia**: Ca activates panc enzymes
- **Genetic**: *CFTR, CTRC, PRSS1, SPINK1, A1AT*
- **Drugs** (<5%): Class Ia: ACEi, dapsone, Lasix, Flagyl, pentamidine, statins, sulfa, tetracycline, valproate, mesalamine; Class Ib: amiodarone, azathioprine/6-MP, dexamethasone; Class II: didanosine, estrogen, propofol, tamoxifen, HCTZ (CGH 2007;5:648)
- **Toxins**: smoking, organophosphates, methanol, scorpion venom
- **Infections**: viral (Coxsackie, EBV, CMV, HIV, Mumps, VZV, HAV, HBV, HSV), bacterial (Mycoplasma, Legionella, Leptospira, Salmonella), fungal (Aspergillus), parasitic (Toxoplasma, Crypto, Ascaris)
- **Ischemia**: vasculitis (SLE, PAN), hypoTN/shock, cholesterol emboli
- **Trauma:** blunt, especially s/p MVA
- **Idiopathic** (10-25%)

DIAGNOSIS (Revised Atlanta Classification: Gut 2013;62:102; Pancreatology 2014;14:324)

- **Presentation**: LUQ/epigastric abd pain (90%, band-like pain to back in 50%), N/V (90%), ileus, jaundice, flank/umbilical ecchymoses
- **History**: prior episodes, EtOH/smoking, prior GI procedures (e.g., CCY, ERCP), meds, infxn sx, autoimmune hx, FH
- **Diagnosis – need 2/3**: 1) consistent clinical presentation, 2) lipase >3x ULN, 3) characteristic imaging (US, CT w/contrast, MRI)
- **Labs**: lipase (*no need to trend*; false ⊕ in CKD, DKA), CBC (often ↑Hct), BMP (Ca), LFTs (↑ALT > 3.5x ULN has 95% PPV for gallstone pancreatitis: AJG 1994;89:1863), lipid panel (TGs). Recheck HCT/BUN <6-8hrs after presentation.
- **Imaging**: All: RUQUS for gallstones; If needed for dx: CT (90% sens), also for complications (~48-72h); MRI/MRCP if c/f necrosis, stricture, or stone w/ neg RUQUS
- **Risk Factors for Severe AP**: +SIRS, Age >55, BMI >30, BUN >20, HCT >44, pleural effusions/infiltrates, extra-pancreatic collections
- **Severity**: mild: absence of organ failure and local or systemic complications; moderate: organ failure that resolves within 48 hours or local/systemic complication; severe: organ failure >48h (22% mortality). Organ failure: can use modified Marshall score
- **Prognosis**: SIRS ↑mortality. Many scoring systems to identify mild type; BISAP is quick/superior. RANSON, APACHE II less practical.

MANAGEMENT (AJG 2024:119(3)e419; WATERFALL trial NEJM 2022; 389:989)

- **IV fluids**: moderately aggressive in 1st 24hrs: infusion 1.5mL/kg + PRN boluses 10mL/kg over 2h if hypovolemic (UOP < 0.5ml/kg/hr or SBP <90). Goal is to not allow Hct or BUN to rise, most pt will benefit from 3-4L in 1st 24hrs. **LR superior to NS**, avoid LR if ↑Ca. Avoid aggressive resus after 24-48h (↑risk of abdominal compartment syndrome, intubation). Ok to d/c at 20 hr if tolerating PO >8hr.
- **Pain control**: IV opioids **Abx**: No role for prophylactic abx.
- **Nutrition**: start PO (low fat/residue) within 24-48h as tolerated. At 5-7d, if PO not tolerated start continuous TFs (NG > NJ). Enteral > TPN: maintains intestinal barrier, prevents gut flora translocation. TPN a/w ↑risk of infections, organ failure/death
- **Reverse precipitants**: treat ↑Ca or ↑TG, stop culprit meds. For gallstone pancreatitis, urgent ERCP (24hrs) if *cholangitis* or CBD obstruction. CCY ideally prior to discharge as ↑biliary complications if CCY is delayed (Lancet 2015;386:1261).
  - **HyperTG**: insulin gtt (0.1-0.3U/kg/hr) + D5, q1h FSBG (initially), q12h TG. Goal TG <500 (may take several days). (MGH ellucid policy) No good evidence for apheresis. If tolerating PO, fibrates are first line. DC: lifestyle Δs, lipid clinic referral
- **If idiopathic:** Repeat RUQUS and triglcyerides as an outpt. If second episode of iAP, recommend cholecystectomy +/- genetic testing

COMPLICATIONS (AGA: Gastro 2020;158:67; NEJM 2016;375:1972)

	Local		Vascular	Systemic
	<4 weeks	**>4 weeks**		
Interstitial edematous pancreatitis	**Acute peripancreatic fluid collection**: w/o features of pseudocyst; resolve spontaneously w/o drainage	**Pancreatic pseudocyst**: fluid collection w/ well-defined wall. If dx unclear, EUS w/ FNA (↑amylase). Drain if sx, rapidly ↑, infxn (endo vs. perc/surg)	**Thromboses**: splenic, portal, SMV; AC if portal vein or bowel ischemia **Pseudoaneurysm**: erosion of GDA/splenic artery → bleeding into pseudocyst. Suspect if ↓Hgb, expansion of fluid collection, unexplained GIB. Dx: arterial phase CT Tx: IR embo. prior to drainage of fluid collection	**Abd. compartment syndrome**: intra-abd pressure >20 w/ new organ failure. Check bladder pressure in ICU. **ARDS**: via phospholipase degradation of surfactant **Metabolic**: ↓Ca, ↑Glc, ↑TG **GIB**: via pseudoaneurysm **AKI** **DIC**
Necrotizing pancreatitis	**Acute necrotic fluid collection**: intra- or extra-pancreatic	**Walled off necrosis**: encapsulated necrotic collection. Drain at >2-4 wks if sx or infxn (endo vs. perc)		
	Infected necrosis: 1/3 become infected, suspect ~7-10d. Early enteral feeding ↓risk Dx: discuss CT-FNA, assume infected if +Bcx/gas. Abx: (cefepime or cipro) + flagyl vs. pip/tazo vs. carbapenem in critically ill. Drainage/necrosectomy: urgent if unstable vs delay >4w if stable on abx			

CHRONIC PANCREATITIS (ACG: AJG 2020;115:322)

Repeat acute attacks (esp. EtOH & smoking) → fibrosis & loss of glandular tissue → chronic abd pain, exocrine insufficiency (steatorrhea, wt loss, vitamin deficiencies), endocrine insufficiency (brittle DM). Lipase/amylase may be ↑ early but nml/low as more tissue lost. ⊕ Fecal fat, ↓stool elastase. CT/MRI with calcifications, ductal dilation, parenchymal atrophy. ↑risk of pancreatic CA. Consider genetic testing. Tx: pancreatic enzyme replacement (Creon), ensure vit ADEK replete, pain control. Refer to MGH Pancreas Center: 617-726-5523

PANCREATIC MASSES (Curr Gastro Rep 2013;15:347)

- Solid: adenoCA (85-90%), autoimmune panc, neuroendocrine (1-5%), 1° lymphoma (<1%), mets (melanoma, RCC, etc.)
- Cystic: inflammatory (pseudocyst, paraduodenal wall cyst), neoplastic (malignant potential: main duct IPMN >> side branch IPMN > mucinous cystic = solid pseudopapillary > serous cystadenoma) (AJG 2018;113:464; Gastro 2015;148:819) Refer to MGH cyst clinic.
- Imaging: **CT abd pancreatic mass protocol**; EUS with FNA for lesions >2-3cm (87% Sn, 96% Sp); MRI useful in <2 cm lesions or when vascular involvement needs to be delineated better; consider PET-CT, MRCP for malignancy in IPMN (70% Sn, 92% Sp)
- Labs: CA 19-9 (⊕ in 80% of panc CA, 86% Sn, 87% Sp), CEA (mucinous), ANA, IgG4 (if autoimmune suspected)

Hailey Harris

Gastroenterology

Weight & Weight Loss

OBESITY

Definition: BMI*: <18.5 underweight; 18.5-24.9 normal weight; 25-29.9 overweight**; 30-34.9 class I obesity; 35-39.9 class II obesity; >40 class III ("severe") obesity**. Avoid using stigmatizing terms such as "morbid" or "extreme"

- Increased waist circumference: >40 inches men, >35 inches women
- *Caveat: studies suggest using a lower BMI criterion for people of Asian descent (AADI BMI calculator)

Epidemiology: 30-45% Americans; Midwest, South > NE, West; non-Hispanic Black > Hispanic > non-Hispanic White > Asian; associated with lower SES, income, education (CDC 2020; NEJM 2019;381:2440).

Associated with: HTN, HLD, T2DM, CAD, stroke, GB disease, OA, sleep apnea, certain cancers, ↑ all-cause mortality

Goal: 5-10% weight loss within 6 months. Benefits at 3-5% weight loss → improved TG, ↓ risk of DM; >5% ↓ →BP, improved BG; 10% decreases fibrosis in MASLD

Treatment:

- Diet: 1200-1500 kcal/d for women; 1500-1800 kcal/d for men; a diet that is 500-750 kcal/day less than usual. Variety of diets – all achieve calorie deficit: balanced low calorie, higher protein, low carbohydrate, low-fat vegan, vegetarian, macronutrient targeted, Mediterranean style, intermittent fasting (Circ 2014;129:S102). Patient choice based on highest likelihood to adhere, comorbidities.
- Lifestyle: comprehensive program – dieting, exercise (effective for weight loss but much more important for weight maintenance), behavioral techniques (Weight Watchers, outpatient programs)
- Meds: *see table.* Indication: wt loss & mgmt. + diet for adults w/ initial BMI ≥30 or BMI ≥27 + wt-related comorbidities (DM, HTN, HLD)

MEDICATIONS FOR WEIGHT LOSS (API 2016;43; JAMA 2016;315:2424; DMI 2020;44; NEJM 2022; 387:205)

Agent	Mechanism of Action	Dose	Side effects	Notes
Semaglutide (weekly, Subq) Liraglutide (daily, Subq) Tirzepatide (weekly, Subq)	GLP-1 receptor agonist (Tirzepatide GLP-1/GIP agonist) (NEJM 2021;384:989) (JAMA 2021;325:1414) (JAMA 2022; 327:138)	Sema: 0.2mg → 2.4mg weekly Lira: 0.6mg → 3mg daily Tirz: 2.5mg → 15mg weekly	N/V/D/C, delayed GE, pancreatitis, cholecystitis. Incr. risk of thyroid cancer in animal models. Contraindicated if personal/FHx of medullary thyroid cancer/MEN2.	**1st line.** Benefit in DM, CAD, MASLD; Potential benefit in HFpEF (NEJM2023;389:1069)
Orlistat (Xenical, Alli OTC)	Inhibit GI lipases that hydrolyze TGs into FFA; increases fecal excretion of TG	60-120mg TID AC	Steatorrhea, fecal incontinence (>10%); reduced ADEK absorption; drug interactions; rare liver/ kidney injury	Reduced BG, lipids, BP; not first-line
Phentermine/topiramate (Qsymia)	Phentermine = stimulant, anorectic, increases satiety by action at the hypothalamus Topiramate = mechanism for weight loss unknown	3.75/23mg x14d → 7.5/46mg x12w; can increase to max 15/92mg	**Teratogenic**. Interacts with metformin. Activating/ insomnia. Paresthesia, constipation, dry mouth, URI, dysgeusia	Should not be used w/ HTN or CAD, caution in anxiety
Naltrexone/bupropion (Contrave)	Works at hypothalamus to increase satiety + inhibition of mesolimbic dopamine (reward) circuit	8/90mg daily 16/180mg BID	Nausea, constipation, HA, vomiting; lower seizure threshold; increase BP; cannot be taken with opioids	Not first line due to side effects, helpful in patients w/ AUD

Choice of agent: GLP1/GIP likely most effective. Greater weight loss with tirzepatide (GLP-1/GIP) vs semaglutide (GLP-1) though no RCTs (NEJM 2022; 387:205). Current data: tirze> sema > lira. If <5% weight loss within 3 months on full dose can try another agent/ med class. Metformin can produce modest weight loss in overweight patients (<5% weight loss) but not FDA approved for weight loss.

WEIGHT LOSS SURGERY (NEJM 2007;356:2176; Lancet 2022;400:441)

Indications: adults with BMI >40 or BMI >35 with obesity-related conditions & who have not responded to behavioral tx w/ or w/o pharmacotherapy. Consider **MGH Weight Center referral**.

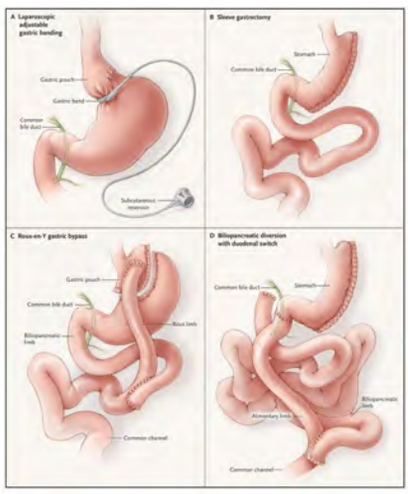
Mechanism of weight loss: restriction (reduced stomach capacity) ± malabsorption (↓nutrient absorption by shortening the absorption length of the small intestine)

Types: Restrictive: sleeve gastrectomy, gastric banding, intragastric balloon; Malabsorptive: jejunoileal bypass (JIB) and biliopancreatic diversion (BPD) ± duodenal switch; Restrictive + malabsorptive: Roux-en-Y gastric bypass (RYGB), single-anastomosis duodenoileal bypass with sleeve gastrectomy

Benefits: 49% (endo sleeve) excess wt lost at 1y vs 3.2% (control) (Lancet 2022;400:441); remission of DM, HTN, HLD, OSA; ↓CV & cancer mortality (30-50%), extended life expectancy by 3 years (NEJM 2020;383:1535; Annals 2020;173:694), improvements in NASH (JAMA 2021;326:2031)

Complications:

- <30d: anastomotic leak, MI, and PE (total 0-1.55%) (Obes Rev 2018;19:529)
- Long term: food aversions/intolerances, **vitamin deficiencies** (**ADEK, Vit C, thiamine, B12, folate, iron, zinc, selenium, copper, Ca**), psychosocial impairment, **dumping syndrome** (rapid transit of hyperosmolar carbs cause fluid shifts, hypotension, sympathetic surge), **osteoporosis**, weight re-gain, increased sensitivity to EtOH



Gastroenterology

Liver Chemistry Tests

Upper Limit of Normal (ULN): ALT (IU/L): 33 (males), 25 (females); ALK-P: 115 (males), 100 (females) (ACG: AJG 2017;112:18)

1) Identify pattern of liver test abnormality. R-factor = (ALT / ULN) / (Alk-P / ULN)
- Hepatocellular: R factor >5, ↑↑ ALT
- Mixed: R factor 2-5, ↑ ALT, ↑ Alk-P
- Cholestatic: R factor <2, ↑↑ Alk-P, ↑↑ GGT, ↑ ALT

2) Identify chronicity
- Acute: < 6 months
- Chronic: > 6 months

Hepatocellular markers: *Released from hepatocytes in response to injury*
ALT: Expressed primarily in liver, **more specific**
AST: Expressed in liver. Also cardiac muscle, skeletal muscle, kidney, brain, and RBCs

Magnitude of ALT and AST elevation:
- **Extreme elevation (>15x ULN or >1,000 U/L):** Most c/w acute liver injury, including ischemic hepatopathy (shock liver), acetaminophen toxicity
- **Moderate elevation (5-15x ULN):** Ddx as above AND acute hepatitis A/B/C/E
- **Borderline to mild elevation (<5x ULN):** Broad ddx: meds/toxins (see below), chronic liver disease (etoh, MASLD, hepatitis B/C, autoimmune, hemochromatosis, Wilson's, alpha-1-anti-trypsin deficiency), biliary obstruction (mixed markers)

AST/ALT ratio: Usually ALT>AST (AST has shorter serum half-life, 18h vs 36h). Ratio can vary widely, especially in acute liver injury
- Mild AST/ALT elevation with ratio ~2:1 suggestive of alcohol related liver dz
- Typical AST/ALT ratio in hepatocytes is 2.5:1, so ratio >2.5:1 think non-hepatic source of AST (Clin. Bio. Rev.; 2013; 34(3)117)

For more info and work-up, *see* ***Acute Liver Injury & Failure***, ***Non-Alcoholic Fatty Liver Disease***, ***Viral Hepatitis***, *and* ***Alcohol Related Liver Disease***

Cholestatic markers: *Released from cells lining bile canaliculi/ducts in response to injury*
Alk-P: Expressed in bile duct, liver, kidney, bone, intestinal mucosa, and placenta. Confirm source with GGT as below or fractionated assay (slow to result). If accompanied by other LFT abnormalities (e.g. elevated bili), do not need to confirm source.
GGT: Expressed in bile duct, liver, pancreas, and kidney. Supports biliary/hepatic source of Alk-P. Non-specific marker of EtOH use.

Magnitude of Alk-P elevation:
- **1-1.5x ULN:** Common in adults over age 60 (esp women 2/2 increased bone turnover)
- **1-3x ULN:** Any liver disease
- **>4x ULN:** Cholestatic liver dz, infiltrative liver dz (e.g. cancer and amyloidosis), bone conditions characterized by rapid bone turnover. In absence of ↑ bili or ALT/AST, suggests early cholestasis or hepatic infiltration by tumor or granulomatous dz

Cholestasis: extrahepatic 2/2 anatomic obstruction to bile flow (e.g. choledocholithiasis, malignancy, PSC, HIV/AIDS cholangiopathy) vs intrahepatic 2/2 functional impairments of bile formation (e.g. PBC, infiltration (sarcoid, atypical fungal infxn, malignancy))

For more info and work-up, see **Biliary Disease**

Markers of liver function:
Bilirubin: Heme breakdown product conjugated in the liver and excreted in bile. Decay is related to albumin half-life (3 weeks).
- Conjugated (direct) bilirubinemia: ↑ **total and direct bilirubin** seen in hepatocellular damage, impaired excretion, or biliary obstruction. Only conjugated bilirubin excreted in urine, so bilirubinuria also implies liver disease. Consider bile duct obstruction/stricture, hepatitis (viral, toxic, EtOH, ischemic, autoimmune), PBC, PSC, infiltrative dz, congestive hepatopathy, TPN, HCC, Rotor syndrome, and Dubin-Johnson syndrome.
- Unconjugated (indirect) bilirubin: ↑ **indirect bilirubin** caused by ↑ production, ↓ uptake by the liver, or ↓ conjugation. Consider hemolysis, hematoma resorption, fasting, ineffective erythropoeisis, and Gilbert syndrome (usually < 3mg/dL).

Albumin: ↓ in chronic liver disorders such as cirrhosis. Not specific to hepatic dysfunction; can also occur in systemic inflammation, nephrotic syndrome, malnutrition, ascites (due to marked increase in plasma volume)
Prothrombin (PT-INR): ↑ PT-INR due to ↓ vitamin K absorption/use 2/2 parenchymal liver disease. PT measures extrinsic coag pathway and relies on vitamin K dependent coag factors. First, consider consumption of clotting factors (e.g., DIC, GI bleed) and meds.
Vitamin K challenge (10mg IV x3 days): If INR normalizes, likely deficiency (e.g., dietary intake, malabsorption [inadequate bile salts needed for Vit K uptake], abx altering gut flora). Vit K supplementation does NOT improve INR in liver disease.
Platelet Count: ↓ platelets associated with ↓ synthesis (liver produces thrombopoietin), splenic sequestration in portal hypertension, and ↑ destruction through multiple pathways.
For more info and work-up, see **End Stage Liver Disease**

Commonly used drugs that cause hepatocellular injury: acetaminophen, allopurinol, amoxicillin-clavulanate, amiodarone, aspirin, carbamazepine, clindamycin, fluconazole/ketoconazole, fluoxetine, glyburide, heparin, hydralazine, INH, labetalol, lisinopril, losartan, methotrexate, niacin, nitrofurantoin, NSAIDs, phenytoin, protease inhibitors, statins, sulfa drugs, trazodone, valproic acid
Supplements: kava-kava, black cohosh, green tea extract, chaparral, ephedra, ji bu huan, germander, weight loss supplements
Illicit drugs: anabolic steroids, cocaine, ecstasy, PCP. **Environmental**: *Amanita* mushrooms
See livertox.nih.gov *for full list* (J Hepatology 2019;70:1222; NEJM 2019;381:264; US Gastro Hep Rev 2010;6:73; AJG 2017;112:18)

Gallstone Diseases (J Hep 2016;65:146)

Cholelithiasis: presence of stones in **GB** (6% of M, 9% of F)	**Choledocholithiasis**: stones in **common bile duct**
- Sx: aSx (<20% develop clinical events), larger, multiple, older gallstones and Female sex ↑events [Gastro 2016;150:156]) vs **biliary colic** (dull RUQ/epigastric pain, 30m-6h, caused by GB contracting around sludge/stone, often postprandial & w/ n/v) - Dx: **RUQUS** (Sn 84%, Sp 99%) > CT (Sn 55-80%); EUS if ⊖; labs wnl - Stone types: *cholesterol* (most common); *pigment*: Crohn's/ileal disease, extravascular hemolysis, TPN - Tx: *asymptomatic*: observe; CCY only if at ↑risk for GB CA (stone >3cm, porcelain GB, GB adenoma); *symptomatic*: elective CCY - Complications: cholecystitis, choledocholithiasis, pancreatitis, GB CA, gallstone ileus, Mirizzi syndrome (compression of CBD/CHD)	- Sx: RUQ pain, n/v, jaundice; may be asx - Labs: ↑ALP, ↑bilis ± ↑AST/ALT - Dx: **RUQUS** to look for CBD dilation >7mm (poor Sn for visualizing stones themselves); **repeat RUQUS**, **MRCP,** or EUS if equivocal - Tx: ERCP w/ stone removal; interval CCY - Complications: ascending cholangitis, acute pancreatitis FYI: can occur s/p CCY if de novo formation in CBD
Cholecystitis: stone in **cystic duct** → inflammation of GB ± infxn	**Cholangitis**: ascending biliary infxn 2/2 **obstruction in CBD**
- Sx: RUQ pain (w/ radiation to back/shoulder), Murphy's sign, n/v, fever - Labs: ↑WBC; +/- ↑ALP, Bili; if ↑↑ALP/Bili c/f CBD obstruction - Acalculous cholecystitis: GB stasis/ischemia w/o obstruction. Unexplained fever, ↑WBC. *RF*: trauma, burns, TPN, severe illness, fasting, sepsis, immunosuppression (CGH 2010;8:15) - Dx: **RUQUS** (GB wall thickening, pericholecystic fluid, *sonographic Murphy's*) → **HIDA** scan if ⊖; pre-tx w/ 2mg IV morphine ↑Sn (given by nuclear rads at MGH) (AJR 2016; 207:865). Tokyo Guidelines for dx & severity (based on deg. of organ dysfunction) (J Hep Panc Sci 2018;25:41) - Tx: **abx** (Zosyn or CTX/Flagyl). **Early (<7d) CCY** during hospitalization → ↓morbidity (Br J Surg 2015;102:1302). If critically ill with biliary sludge and ↑LFTs or high surgical risk & fails to improve after 1-3d abx → **percutaneous cholecystostomy with IR**. Stop abx 24h post-CCY unless septic/perc chole: 4-7d (JAMA Surg 2019;154:873) - Complications: gangrenous cholecystitis, emphysematous cholecystitis (gas-forming organism), perforation, enteric fistula, gallstone ileus	- Etiologies: stone, stricture (malignancy, PSC, AIDS), liver fluke - Sx: *Charcot's triad:* RUQ pain, fever, jaundice; *Reynold's pentad*: + shock and AMS - Labs: ↑WBC, ↑ALP, ↑Bili, ± ↑AST/ALT (can be ↑↑) - Dx: **RUQUS** (ductal dilation), **MRCP**/ERCP. Tokyo Guidelines for dx & severity (J Hep Panc Sci 2018;25:17) - Tx: broad spectrum **abx** (Zosyn or CTX/flagyl; carbapenem if life-threatening) x7d; urgent **ERCP** w/ decompression (<24-48h) if severe (associated organ dysfunction/shock) or if fails to improve on abx x 24h. Perc drainage if ERCP not feasible. Interval **CCY** if due to gallstones - Higher risk for cholangitis after palliative CBD stent placement in patients with malignant obstruction - Complications Post-ERCP: pancreatitis, bleeding, infxn, perforation (GIE 2017;85:32)

Autoimmune Biliary Diseases

Primary Biliary Cholangitis (PBC) (AASLD: Hepatology 2019;69:394)	**Primary Sclerosing Cholangitis (PSC)** (AASLD: Hepatology 2022)
Autoimmune destruction of *intrahepatic* bile ducts	Affects *intra-* + *extrahepatic* bile ducts
- Clinical manifestations: F>M; asx (50-60%), pruritus, fatigue, sicca symptoms, cirrhosis (late) - Dx: ≥2 *of the following*: **ALP** ≥1.5x ULN; **Antimitochondrial Ab**>1:40 titer (95% pts); biopsy findings; can have AMA (-) PBC - Biomarkers: SPATA31A3 and GARP (Liver Int. 2019;39:2124) - Associated with: **hypothyroidism** (20% pts), anemia, metabolic bone disease, Sjogren's, autoimmune hepatitis (overlap) - Tx: **ursodiol**: 1st line, ↓progression & ↑survival (NEJM 1994;330:1342); **obeticholic acid** (FXR agonist) 2nd line after ursodiol, C.I. in decomp ESLD & portalHTN, **fibrates**: off label altern, C.I. in decomp ESLD; **cholestyramine** for pruritus; **modafinil** for fatigue; **liver transplant**: 22% recurrence in 5yrs	- Clinical manifestations: M>F; asx (50%), pruritus and fatigue (most common), cirrhosis (late); cholangitis due to strictures - Dx: ↑ALP ± bili; may have +auto-Abs but of unclear significance; MRCP (segmental strictures**)**, ± biopsy if suspect small duct PSC (otherwise not required); check AMA/IgG4 to exclude alt. dx - Associated with: **IBD** (60-80%; UC>Crohn's), **cholangioCA** (10-15% pts), metabolic bone disease, AIH (overlap), HLA-83 - Tx: *supportive;* ursodiol may improve sx, ERCP for stricture, **liver transplant definitive tx** (MELD exceptions for recurrent cholangitis, intractable pruritus): 20% recurrence 5 years post-LT - Hepatobiliary CA surveillance q6-12 month (imaging, CA 19-9, AFP) improves survival (Hepatology 2018;67:2338)

Malignant Disease of the Biliary Tract

Gallbladder carcinoma: risk factors: gallstone disease (34x more likely to develop CA), porcelain GB, GB polyps, PSC, chronic infxn

- Diagnosis: LFTs usually normal, ↑CA19-9/CEA; RUQUS best screening test, then CT/MRI/MRCP

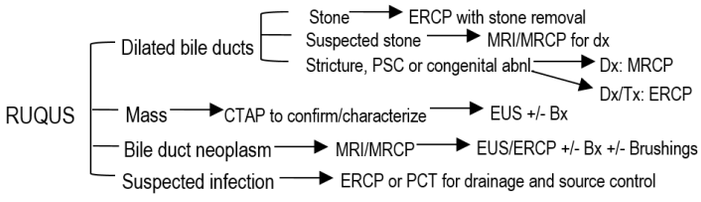
Cholangiocarcinoma: may be extrahepatic (90%) or intrahepatic (10%); risk factors: PSC, liver flukes, intrahepatic gallstones

- Diagnosis: ↑ALP, bili, CA 19-9/CEA ± ↑AST/ALT depending on deg. of obstruction; RUQUS screening test, then ERCP/MRCP/EUS

Sphincter of Oddi Dysfunction

F>M; Often occurs post-CCY, provoked by opioids (due to spasm of sphincter) and associated with idiopathic recurrent pancreatitis, Rome IV criteria (MD Calc). Diagnosis: ERCP/manometry. Treatment: surgical/endoscopic sphincter ablation (Curr Gastro Rep 2015;17:31)

Radiographic Assessment of Suspected Biliary Pathology (Am J Roentgenol 2011;197:551)



Gastroenterology

Acute Liver Injury & Failure

Acute Liver Injury (ALI): **acute liver injury <26w with coagulopathy but NOT encephalopathy**
Acute Liver Failure (ALF): **encephalopathy & coagulopathy (INR >1.5) of <26w in pts without cirrhosis or known liver disease**

Presentation: fatigue, lethargy, anorexia, n/v, RUQ pain, pruritis, ± jaundice → ascites, confusion in ALF (and may progress to coma)
Initial diagnostics: CBC w/ diff, CMP, PT/INR, fibrinogen, LDH, T&S, lactate, ABG, arterial ammonia, FSBG, hCG, HIV, APAP, blood/urine tox screen, PETH, viral/autoimmune serologies (as below), amylase/lipase, CT head if HE, RUQUS w/ Doppler (JHM 2017;12:184)

Type	Etiologies	Diagnostics
Drugs (see LiverTox)	Acetaminophen (dose-depend: >6g/day or 150/mg/kg/day for 24-48h, >4g/day or 100 mg/kg/day for >48h): most common cause of ALF in US Toxins: *Amanita phalloides* mushroom, occupational exposures (CCl_4) Idiosyncratic DILI (dose-indep): abx (*Augmentin), AEDs, anti-TB, etc. (Alcohol-related hepatitis: considered acute-on-chronic and *not* ALF)	History: all APAP-containing meds, herbal supplements, new meds/OTCs, EtOH use Labs: APAP level, EtOH, tox screen
Viral	HAV, HBV, HCV (rare w/o HBV co-infection), HDV (↑risk co-infection > superinfection or HBV alone), HEV (pregnant or in endemic areas) Others: HSV (may be anicteric, ↓WBC), adenovirus, EBV, HIV, CMV, VZV (if immunocompromised)	History: travel, PWID, occupational exposures, sexual exposures, vesicular rash, blood transfusion, immunocompromised state Labs: HAV IgM, HBsAg & core IgM, HCV Ab & PCR, HSV Ab; check HDV if +HBV, HEV if preg., VZV if immunocompromised, EBV PCR
Ischemic/ vascular	Systemic hypoTN (sepsis, cardiac dysfunction), vasoconstricting drugs (cocaine, meth.), Budd-Chiari (hepatic vein thrombosis), veno-occlusive disease (post-HSCT); ALT/LDH <1.5 suggestive of ischemic	History: HoTN, hypercoag. state, drugs/meds Imaging: RUQUS w/ Doppler; CT or MRI/MRV are alternatives; consider TTE if no known cause
Autoimm.	AIH: F>M; can present as ALF but uncommon	Labs: IgG (↑), ANA, ASMA, anti-LKM-1
Genetic	Wilson's: <40, F>M; AST>ALT often >2; nml/↓ALP & ALP/Tbili <4; a/w DAT-neg. hemolytic anemia, ↓uric acid, rapidly progressive renal failure	History/exam: FH, slit-lamp exam for KF rings Labs: ceruloplasmin (though may be nml/↑ in ALF)
Others	HELLP, acute fatty liver of pregnancy, malignant infiltration (breast CA, SCLC, lymphoma, myeloma), HLH, heat stroke, hepatectomy	Labs: U/A if pregnant Liver bx if dx remains elusive after thorough eval

Management of Acute Liver Failure (AASLD: Hep 2012;55:965; AGA: Gastro 2023;118:1128; NEJM 2013;369:2525)

- **Consult Hepatology for OLT workup.** Urgency based on HE severity (ASAP if grade 3-4)
- Monitoring: freq. coags, CBC, ABG, CMP, NH_3; q2 hr neuro checks to monitor for worsening HE or ↑ICP (esp. gr. 3-4), e.g., Cushing's triad (bradycardia, irregular respirations, and wide pulse pressure) requiring more intensive monitoring.
- Hemodynamics: IVF (NS) and/or pressors (norepi ± vaso); goal MAP ≥75 for cerebral perfusion
- N-Acetylcysteine (NAC): tx APAP toxicity ± non-APAP ALF w/ gr 1-2 HE (Gastro 2009;137:856). Initial tx: 150mg/kg/h, 1h, max 15g→ 12.5mg/kg/h, 4h, max 5g→ 6.25mg/kg/h, 16h, max 10g
- **Encephalopathy**: intubation for HE gr. ≥3; **↑cerebral edema** in HE gr. 3 (25-35%) & 4 (75%)
  - Lactulose in ALF controversial: ↑bowel distent. may worsen outcomes
  - CRRT lowers ammonia levels within 3 days and decreases mortality (Hep 2018;67:711)
  - If **↑↑risk** for cerebral edema (gr. 3-4, aNH3 >150, ARF, pressors), **prevent** w/ 3% NaCl for Na 145-155 (Hep 2004;39:464), HOB 30°, ↓stimulation; avoid: overhydration & ↑PEEP
  - Treat cerebral edema w/ IV mannitol (0.5-1g/kg bolus x1-3); if impending herniation, hyperventilate to PaCO2 ~25-30 (temporary; may worsen edema by → ischemia); pentobarbital/thiopental if other measures fail (may cause hoTN which → ↓CPP)
- Seizures: phenytoin; benzos if refractory. Consider routine EEGs for subclinical seizure
- Infection: high risk for bacterial (Staph, Strep, GNRs) & fungal. Check serial BCx, UCx, SCx, CXR. May not fever, ↑WBC, or have localizing s/s, though worsening HE or AKI may be sign. Low threshold for empiric abx ± antifungal (esp. if prolonged hosp., abx, steroids, CVVH). Avoid nephrotoxic/hepatotoxic abx
- Coagulopathy/bleeding: can trial vit K, routine FFP not recommended. In ICU, ppx w/ PPI. Viscoelastic tests (e.g., TEG) may be more accurate assessment of coagulopathy

Hepatic Encephalopathy		
Grade	Mental Status	Asterixis
I	Attention deficit	±
II	Lethargy Moderate confusion	+
III	Somnolence Marked confusion	+
IV	Coma	+

Complications of Acute Liver Failure	
Neuro	HE, cerebral edema
CV	Shock, high-output state
Pulm.	Pulm. edema, ARDS
GI	GIB, pancreatitis (esp. APAP)
Endo.	↓Glc, adrenal insuff.
Renal	Renal dysfxn in >50%; met. acid. (↑lactate), ↓Na, ↓K, ↓P
Heme	Coagulopathy, ↓plt, DIC
Infection	In ~90%; bacterial + fungal

Etiology-Specific Management

- APAP → Ingestion <4h or rising level, give activated charcoal. Ingestion >30g or deranged AST/ALT, give empiric NAC. See Figure 1: treatment pathway, Figure 2: revised nomogram, Figure 3: NAC guidelines in *Consensus Statement*: JAMA 2023;6(8)e2327739
- HBV/HCV → OLT; possible role for antivirals in HBV
- HAV/HEV → supportive care, possible OLT
- Amanita poisoning → IV silibinin (20-50 mg/kg/d x2-4d)
- AFLP/HELLP → delivery; follow up for need for OLT
- HSV/VZV → acyclovir (5-10mg/kg q8h); may need OLT
- AIH → consider glucocorticoids; OLT if needed
- Wilson's → OLT; chelation ineffective
- Budd-Chiari → anticoag, TIPS, surg decompression, lysis, OLT

King's College Criteria (specific but not sensitive)– list for OLT if:
- **Acetaminophen-induced ALF:** Arterial pH <7.3 OR **all 3** of: INR >6.5, Cr >3.4, grade 3-4 HE
- **Other causes of ALF:** INR >6.5 OR **3/5**: age<10 or >40, Tbili ≥17, INR >3.5, time from jaundice to encephalopathy >7d, unfavorable etiology (seronegative hepatitis, DILI, Wilson's)

Prognosis: MELD score >25 = poor prognosis. HBV, Wilson's, Budd-Chiari, AIH, DILI also associated with poor prognosis.

Gastroenterology — Viral Hepatitis

HEPATITIS A (CDC 2020)

Fecal-oral transmission from personal contact or contam. food/water, international travel. Sx: abrupt n/v, anorexia, malaise, fever, jaundice, RUQ/abd pain, ↑ALT>AST (often >1000), ↑bilirubin/ALP. 70% of adults have sx, lasts 2-8w (often self-limited), jaundice peaks after 2w. Dx: ⊕ anti-HAV IgM, persists 3-6mo, or RNA. Anti-HAV IgG forms at 2-3w, confers immunity. Tx: Care is supportive unless ALF (rare,<1%). Vaccinate if: MSM, PWID, chronic liver dz, HIV, travel, homeless, certain exposures. Havrix and Vaqta = 2 doses. Twinrix = 3 doses, covers HBV. Pre and post-exposure ppx: Single HAV vaccine +/- immune globulin in non-immune pts w/in 2 wks of exposure.

HEPATITIS B (AASLD: Hepatology 2018;67:1560; USPSTF: JAMA 2020;324:2452)

Screening	HBsAg. Pts from area w/ prev. ≥ 2%, parents from high prev. area ≥8%, HIV+, PWID, MSM, close contact of HBV+ person, unexplained elevated LFTs, those requiring immunosuppressive therapy (e.g. done before chemo)
Risk Factors	Vertical transmission (SE Asia), sexual contact, PWID, needlestick, unvaccinated (US before 1994), immunosuppress.
Clinical Pres.	**Acute**: 70% subclinical, 30% w/ jaundice, <1% ALF. S/S: anorexia, nausea, fatigue, RUQ discomfort. ALT>AST in 1000s, +/- ↑Bili. **Chronic**: ⊕HBsAg >6mo. (often w/ persistent ↑ALT), occurs <5% adults. 40%→cirrhosis
Extrahepatic	Polyarteritis Nodosa, membranous nephropathy/MPGN, aplastic anemia, arthritis
Diagnosis	HBsAg, anti-HBs, anti-HBc total (identifies all infected). Interpretation below
Treatment	First line: tenofovir or entecavir (Hepatology 2018;67:1560) PegIFN option for young w/o cirrhosis for a finite treatment course. Monitor HBV DNA, LFTs, Cr while on therapy. **Goal**: suppress HBV DNA, lose HBsAg & HBeAg
HCC Screen.	**Indications**: all HBsAg+ w/ cirrhosis, HBsAg+ & high-risk (Asian/Black M >40; Asian F >50; +HDV; +FH HCC)

HBsAg	Anti-HBs	Anti-HBc (total)	Interpretation	Next Steps
⊕	-	⊕	Hepatitis B infected (acute or chronic)	Check anti-HBc IgM (acute vs. chronic), HBV DNA, HBeAg, total anti-HDV
-	⊕	⊕	Past infection (resolved)	None; ↑ risk of reactivation w/ chemo/immunosuppression
-	-	⊕	(1) Recovery from remote acute infxn (w/ anti-HBs titers that have waned), (2) chronic infxn (& low level HBsAg), (3) acute HBV in window period, (4) false ⊕ anti-HBc *or* false ⊖ HBsAg	Differentiate possibilities w/ anti-HBc IgM (acute infxn vs. others), anti-HBe, HBV DNA, repeat anti-HBc (later). "occult HBV" = DNA⊕ w/ HBsAg⊖ +/- HBcAb⊕. Low risk reactivation but ↑ if chemo/immunosuppression
-	⊕	-	HBV-immune from prior vaccination	None
-	-	-	Uninfected, non-immune	Vaccinate. Engerix-B (3 doses, at 0,1,6mo). *NB:* If receiving HD, double dose, at 0,1,2,6mo

HBV reactivation: indicated by: (1) ↑ in HBV DNA vs. baseline or (2) reverse seroconversion from HBsAg-/anti-HBc+ to HBsAg+. **Check serologies before high-risk therapies**: rituximab, anti-TNF, high dose steroids (>20mg pred/d x4w), HSCT, chemotherapy, anti-rejection therapy. HBsAg+ is greatest risk, need ppx. HBsAg-/anti-HBc+ is lower risk, ppx vs monitor for reactivation

Management: *Acute*: unless severe, supportive. *Chronic*: tx if decompensated cirrhosis or if compensated w/ DNA >2k (& consider if <2k) regardless of ALT to ↓ risk of decompensation. If no cirrhosis, depends on eAg/ALT/DNA level (see p.1571 Hepatology 2018;67:1560)

HEPATITIS C (AASLD/IDSA: CID 2023 https://www.hcvguidelines.org/)

Screening	HCV Ab. If positive, order RNA Viral Load (PCR), MGH does not have reflex testing. **Everyone: *universal one-time screening*** (CDC: MMWR Rec Rep 2020;69:1; USPSTF: JAMA 2020;323:970). IVDU or MSM w/ HIV: annual
Risk Factors	IVDU, blood products pre-1992, MSM, HIV, chronic HD, incarceration, immigration from ↑prevalence area, HCV infected mother, sex with HCV+ partner
Diagnosis	⊕Ab, ⊕RNA = current infection. ⊕Ab, ⊖RNA = cleared or treated (can still get reinfected)
Natural History	Acute HCV: 75% subclinical. If sx, develop 2-26w after exposure, last 2-12w. Fulminant rare (<1%) Chronic HCV: 80% → chronic; if younger, female sex, genotype 1, IL28B, jaundice, ↑ALT more likely to clear spontaneously 20% → cirrhosis (↑risk if male sex, EtOH, obesity, HIV, immunosupp.). HCC risk 1-13%/yr
Extrahepatic	Mixed cryo., porphyria cutanea tarda, lichen planus, LCV, thyroiditis, Sjogren's, renal dz (e.g., MPGN), NHL
Treatment	1) Assess advanced fibrosis with FIB-4 score, U/S Elastography (FibroScan), FibroSure 2) Obtain HIV test (if +, initiate ART 1st), HBsAg (tx if applicable), and Upreg neg. Get CBC, LFTs, GFR baseline 3) Confirm pt eligible for simplified tx. Eligible if: compensated cirrhosis, no prior HCV tx; NOT eligible if cirrhosis AND eGFR <30, HBsAg (+), pregnant, prior liver transplant, c/f HCC. Consider GI/ID referral if not eligible 4) If eligible for simplified tx: If no cirrhosis, start pan-genotypic Rx: Mavyret (Gle/Pib) x8wks or Epclusa (Sof/Vel) x12wks. If +compensated cirrhosis, genotype guides therapy unless using Gle/Pib which works for all genotypes. Monitoring: If on warfarin, monitor for subtherapeutic INR. Monitor for hypoglycemia w/ DM meds. ***Note: patients DO NOT need to abstain from drugs or EtOH***. (AASLD, IDSA 2020).
Follow-up	HCV RNA and LFTs >12 wk after Tx to assess SVR. If cirrhosis, continue HCC surveillance/variceal screening (q6mo U/S, EGD) EVEN after SVR. If no SVR at 12 wk, ID/GI referral and assess for fibrosis q6m (LFTs/CBC/INR)

HEPATITIS D (Gastro 2019;156:461)

Coinfection with HBV similar to HBV but more severe, ↑risk ALF; often biphasic ALT course. Superinfection on HBV most severe, highest risk ALF & chronic infxn (90%) → cirrhosis in 80% in 5-10y. 3x ↑risk HCC vs. HBV mono-infection. Check total anti-HDV once in all HBV infected patients (usually appears after 4 weeks). If suspect false negative Ab, confirm with HDV RNA PCR

HEPATITIS E (APT 2017;46:126; Gastro 2012;142:1388)

Most common cause of viral hepatitis in endemic areas. Transmission: fecal-oral, vertical, zoonotic (swine organ meats). Most asx, resolve spontaneously. Extra-hepatic: neuro (e.g., GBS), renal, arthritis, anemia, pancreatitis. ↑risk of ALF/mortality in pregnant women (Annals 2007;147:28). Rarely chronic HEV in transplant recipients. Dx: HEV IgG+ IgM, high false ⊕/⊖. Tx: supportive care (if immunocompetent)

Christian Bonilla

ALCOHOL-RELATED LIVER DISEASE (ALD) (AASLD: Hepatology 2020;71:308; ACG: AJG 2024;119:30)

Risk factors: sex (F>M), pattern (↑daily ± ↑binge), obesity, DM2, genetics (e.g. PNPLA3, α-1 antitrypsin, TM6SF2, MBOAT7), smoking, comorbid HCV/MASLD/etc.; coffee ↓risk. Harmful drinking: Men: ≥3 drinks/d or ≥21/wk. Women: ≥2 drinks/d or ≥14/wk

Pathophysiology: EtOH → fat accumulation; EtOH → ↑gut permeability → ↑innate immune response, liver cell inflammation, injury, necrosis, fibrosis; may be important role for gut microbiota (Nature 2019;575:505)

Disease spectrum:

- Steatosis: usually asx; may have mild ↑AST>ALT, GGT; develops in 90% w/ >60g/d EtOH after 2w; reversible w/ 4-6w abstinence
  - 20-40% develop fibrosis → 8-20% to cirrhosis → 20-40% decomp/acute-on-chronic liver failure; HCC in 3-10% w/ cirrhosis
- Steatohepatitis: histopathologic correlate of AH; can develop at any stage of ALD; often → to fibrosis (40-50%) & cirrhosis (>75%)
- Alcohol-related hepatitis (AH): an acute inflammatory syndrome that can occur at any stage of ALD
- Cirrhosis due to ALD: pathologic fibrosis distorting liver architecture, resulting in abnormal blood flow

Prognosis: 5-year mortality due to liver disease is 25.8%. (Lancet;8:1028)

Treatment: Motivational interviewing, CBT, and behavioral intervention (5 "A" model: ask about use, advice to quit/reduce, assess willingness, assist to quit/reduce, and arrange f/u). Pharmcology: Baclofen, acamprosate or naltrexone, gabapentin or topiramate. Suggest against disulfram, C.I. in liver disease. (*See AUD*)

Alcohol Liver Evaluation Team (ALiVE, p26299): eval. inpts w/ ALD or AUD w/o known ALD admitted for non-liver related complaints. Goal earlier identification of subclinical advanced fibrosis and connection to hepatology team for treatment.

ALCOHOL-RELATED HEPATITIS

Presentation: varies from few sx to liver failure; jaundice, anorexia, fever, abd pain (tender hepatomegaly), malaise, weakness, nausea

- Can lead to portal HTN & its sequelae (EVs, ascites, HE) in the absence of cirrhosis due to hepatic swelling & portal venous obstruct.

Dx: jaundice w/in prior 8w, ongoing heavy EtOH (F >3 std. drinks/d, M >4 std. drinks/d for >6mo). <60d abstinence before onset of jaundice, AST moderate ↑ (50-400) w/ AST/ALT >1.5, Tbili >3. Often ↑WBC (<20k, ↑PMNs), ↑INR

- Must exclude other etiologies of acute hepatitis/jaundice (viral, meds/herbs, ischemia, AIH, Budd-Chiari, biliary obstruct.), decompensated cirrhosis; can be superimposed in 10-20% (Alcohol CER 2004;28:31). Check HAV/HBV/HCV, APAP level, US w/ Doppler, ± (ANA, ASMA, IgG levels, AMA). Assess for signs of cirrhosis
- Transjugular Bx: consider if atypical presentation and/or labs (e.g., AST/ALT >400), uncertain alcohol intake hx, jaundice >3 months, or suspicion for alternative etiology, such as use of hepatotoxic meds, possible ischemic insult (e.g., HoTN, cocaine use), etc.

Exclude infection: May have SIRS/fever due to inflamm., but screen for infxn as at high risk (esp. if severe AH: 12-26% at admission)

Prognostic Tool	Use	Components	Stratification
Maddrey Discriminant Function (MDF)	Identify who will benefit from steroid therapy	PT, PT control (14.5 at MGH), Tbili	≥32 = severe → 1mo. mortality 30-50%; GI consult re: steroids (Gastro 1978:75:193)
MELD		Tbili, INR, Cr, Na	>20 = inpt admission, 3mo. mortality 20%; Consult GI for steroids (Hepatology 2005;41:353)
Lille	Perform on day 4 & 7 to assess steroid response	Day 0: Age, Albumin, PT, Cr Day 0, 4, & 7: Tbili	≥0.45: Nonresponse → stop steroids <0.45: Response → continue steroids (Hepatology 2007;45:1348)

TREATMENT OF ALCOHOL-RELATED HEPATITIS

Corticosteroids: see algorithm

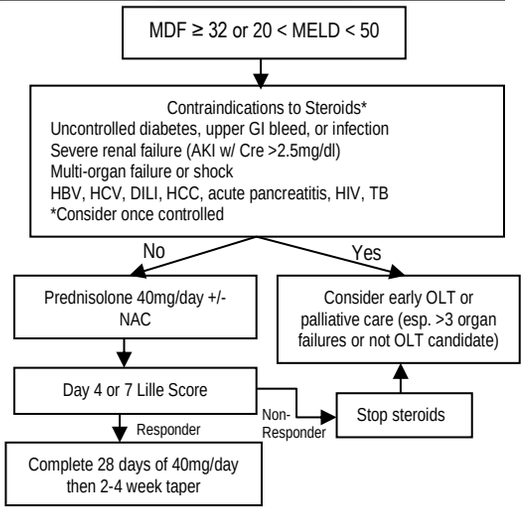
- Prednisolone used as not metabolized by liver (methylpred 32mg is IV alternative): 40mg x 28d w/ 2-4w taper. Lille score at 4 or 7 days to assess steroid response.
- No mortality difference at 28d or 90d, ↑infxn (NEJM 2015;372:1619).

NAC: may benefit, no harm (though is large volume load) x5d

Supportive therapy: hold βB if MDF ≥32 as ↑AKI incidence (Liver Int. 2015;35:8)

Nutrition: Goal 35 kcal/kg/d with 1.2–1.5 g/kg of protein; supplement w/ MVI, thiamine, folate, B6, B12, and Zn. Low kcal in severe AH a/w ↑infxn (Gastro 2016;150:903). Nutrition consult. If <21 kcal/kg/day, consider TF w/ NGT.

Abstinence: can result in rapid improvement in outcomes w/in 3mo. Combination of psychosocial + pharmacotherapy achieved best outcomes (J Hepatol 2016;65:618). Age and lack of past alcohol use treatments were independently associated with complete abstinence (Hepatology 2017;66:1864)



LIVER TRANSPLANTATION:

Definitive therapy for ALD. Traditionally required 6mo abstinence. ↑6mo survival with low risk of alcohol relapse and low impact on donor pool in appropriately selected pts (NEJM 2011;365:1790, Am J Transplant 2016;16:841)

- **MGH** offers early LT eval. prior to 6 mo. abstinence for pts w/ 1) 1st alcohol-related decompensating event (i.e., no prior knowledge of alcohol-related liver disease or alcohol-related legal issues), 2) maddrey discriminant function (MDF) ≥32, 3) no response to steroids, 4) no grade 3-4 HE (to allow for psych eval), 5) strong social support, 6) no severe psychiatric co-morbidities, and 7) no other SUD. Consult hepatology for candidacy. Can discuss if candidate at MELD >10 to give time for education/evaluation.

Other therapies with potential efficacy:

- **NAC**: w/ steroids x5d, may ↓mortality at 1mo, not 3 or 6mo (NEJM 2011;365:1781, Gastro 2015;149:958)
- Pentoxifylline: Not recommended. Consider if steroids contraind, no convincing data on ↓mortality, but does↓AKI/HRS (Gastro 2000;119:1637, APT 2013;37:845)
- G-CSF: in clinical trials (Hepatology 2019;70:802, AJG 2014;109:1417)
- Fecal transplantation: Small RCT, ↓ 90d mortality but risk of donor related infx (Hepatol Int 2023;17(1):249)

Gastroenterology MASLD

DEFINITIONS (Hepatology 2023;78:1966)

Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD): presence of hepatic steatosis (imaging or bx) w/o 2° cause (includes NASH)
Metabolic dysfunction-associated steatohepatitis (MASH): hepatic steatosis and inflammation with hepatocyte injury ± fibrosis
Metabolic and alcohol related/associated liver disease (MetALD): metabolic dysfunction + 140-350 g/wk or 210-420 g/wk of alc for female and male respectively.
MASH cirrhosis: cirrhosis with current or previous histological/clinical evidence of steatosis or steatohepatitis

EPIDEMIOLOGY (Gut 2018;67:963; CLD 2016;8:100; J. Hepatol 2022;77:1237)

- **Prevalence**: 10-46% in US; >95% in pts w/ obesity undergoing bariatric surg, 33-66% in pts w/ T2DM, and 50% in pts w/dyslipidemia, ↑ with ↑TC:HDL & TG:HDL (but growing number of lean MASLD)
- **Risk factors for progression**: insulin resistance, DM, weight gain, HTN, AST/ALT >1 (JAMA 2015;313:2263)
- Progression rates: MASLD → cirrhosis: 3% in 15 yrs, compensated cirrhosis to first decompensation: 33% in 4 yrs.

DIAGNOSIS (NEJM 2017;377:2063; Hepatology 2018;67:328; Hepatology 2011;54:344)

- **Presentation**: mild ↑AST, ALT (2-4x ULN with AST:ALT ratio <1) or imaging w/ hepatic steatosis (~70% w/ nl LFTs)
  - No indication for routine screening in high-risk pts due to limited tx options. However, maintain high index of suspicion in those with RFs (CLD 2021;17.1:23)
- **History & Physical**:
  - DDx: EtOH use, viral hepatitis, parenteral nutrition, Wilson's disease, malnutrition, hemochromatosis, autoimmune liver disease, α-1 AT deficiency, DILI, celiac disease, thyroid disease. Uncommon: hypobetalipoproteinemia, LAL deficiency, carnitine/choline deficiency
  - Screen for significant EtOH consumption (>21 standard drinks/wk in men, >14 in women)
  - Evaluate for associated comorbidities (T2DM, obesity, central adiposity, dyslipidemia, hypothyroidism, PCOS, OSA)
  - Assess for signs of cirrhosis and insulin resistance (e.g., acanthosis nigricans)
- **Labs**: LFTs, CBC, PT/INR, HCV Ab, lipid panel, HgbA1c, celiac serologies, TSH
  - If elevated LFTs: consider iron studies, α-1AT, ANA, ASMA, SPEP, HBV
    - Ferritin may be ↑ in hemochromatosis and MASLD, so if iron sat also elevated, consider HFE testing
- **Imaging**: ultrasound to confirm hepatic steatosis, rule out other pathology
  - Non-invasive evaluation for advanced fibrosis (F3-4); assess q3y – if indeterminate, consider 2nd test including liver biopsy (J Hepatol 2015;63:237; Hepatology 2019;70:1521; DDS 2016;61:1356; Hepatology 2018;67:260)

Diagnostic	Considerations	Rule Out	Rule In
NAFLD fibrosis score (NFS)	Use to triage pts 35-65yo w/ ↓risk of advanced fibrosis & monitor progression; quick but not liver-specific. If clinical suspicion for metabolic liver disease, FIB-4 recommended in every 1-2 yrs in pre-DM2/DM2 or 2+ metabolic RF vs every 2-3yrs if <2 metabolic RF	< -1.455 (Sn 90%, Sp 60%)	≥ 0.676 (Sn 67%, Sp 97%)
FIB-4		< 1.3 (Sn 82%, Sp 57%)	> 2.67 (Sn 36%, Sp 93%)
VCTE (FibroScan)	Most used/validated; high user variability, limited in pts w/ severe obesity and ascites	< 9.9 kPa (Sn 83%, Sp 61%)	≥ 11.4 kPa (Sn 75%, Sp 71%)
Ultrasound elastography	Similar to FibroScan, also provides imaging; obtain if need for ultrasound	< 7.1 kPa (Sn 94%, Sp 52%)	> 9.2 kPa (Sn 93%, Sp 81%)

- **Referral to Hepatology**: persistent/significant transaminase elevation (ALT >30), advanced fibrosis, need for liver bx
- **Biopsy**: for pts with F3 or > on non-invasive imaging, at high risk of advanced fibrosis/MASH or competing etiologies of liver disease (CLD 2021;17.1:23)

MANAGEMENT (CLD 2020;15:4)

- **Lifestyle intervention**: weight loss is 1° therapy. ≥5% reduces hepatosteatosis; 7-10% may improve fibrosis (target ↓ 500-1000 kcals/d); Mediterranean diet, low carb, higher protein diet associated w/ improvement in weight loss; reducing fructose consumption helpful; exercise can significantly improve insulin resistance & outcomes (see *weight loss* for med. options). Abstain from excessive alcohol use.
- **Pharmacotherapy:** pioglitazone improves histology; vitamin E 800IU/d improves histology in pts without DM in bx-proven MASH (PIVENS trial, NEJM 2010;362:1675); omega-3 FAs improve hyperTG in pts with MetALD (APT 2010;31:679); GLP-1ra: semaglutide in pts with F2/F3 fibrosis to ↑MASH resolution w/o improved fibrosis (NEJM 2021;384:1113). SGLT-2i reduce steatosis on imaging.
  - Not recommended currently: metformin (give if T2DM for ↑weight loss), UDCA, obeticholic acid, elafibranor
- **Surgery**: consider bariatric surg in eligible pts with obesity and MASLD or MASH
- **Other considerations**: Prevent progression of liver disease – vaccinate for HAV/HBV, avoid EtOH consumption. Treat comorbidities (T2DM, HLD, HTN) Statins are recommended in MASLD for CVD risk reduction.

Gastroenterology — End Stage Liver Disease

DEFINITIONS

- Cirrhosis: irreversible fibrosis and formation of regenerative nodules that distorts hepatic architecture and vasculature
    - Compensated: no ascites, encephalopathy, jaundice, or GI bleeding. May have nonbleeding varices. Usually asx
    - Decompensated: ascites, HE, jaundice, SBP, Hepatopulmonary syndrome, variceal bleeding or HRS
- End-stage liver disease (ESLD): accompanying pathophysiologic state of impaired liver function

CLINICAL MANIFESTATIONS AND DIAGNOSIS (JAMA 2012;307:832)

- **Symptoms**: fatigue/weakness, jaundice, pruritus, nausea, anorexia, abdominal distention, GIB, confusion, muscle cramps
- **Exam**: ↓BP, splenomegaly, caput medusae, ascites (+LR 7.3), jaundice, spider angiomata (+LR 4.3), gynecomastia, testicular atrophy, palmar erythema, asterixis, white nails, Dupuytren's contracture
- **Labs**: ↑TBili, ↑INR, ↓alb, ↓Na, ↓PLT (<160, +LR 6.3), ± ↓Hgb/Hct, ↓WBC; AST, ALT, alk phos, and GGT may be ↑ or normal
- **Diagnostics**: viral hepatitis panel, iron studies, ANA, ASMA, AMA, α1AT, ceruloplasmin
- **Imaging**: RUQUS (with Doppler) to assess echogenicity/morphology of liver, ascites, vascular patency, biliary tree, HCC; US elastography measures liver stiffness by applying mechanical waves and measuring propagation speed through tissue
- **Biopsy**: gold standard but performed less often. Main indications are dx uncertainty or indeterminate fibrosis severity (NEJM 2017;377:756). Perc. (cannot do through ascites, massive obesity) or transjugular (allows HVPG measurement; pref. if coagulopathy)

ETIOLOGIES

- **Most common**: metabolic associated liver disease (metAFLD), alcohol, viral (HCV, HBV). Global epi: metAFLD (54%), HBV (29%), HCV (9%), ALD (2%) (*CLD* 2021; 17:365): in the US, ALD a much higher proportion.
- Genetic disorders: hemochromatosis, Wilson's, α1AT deficiency, CF, inherited disorders of glucose metabolism, hypobetalipoproteinemia, LAL deficiency
- Immune-related: autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), celiac disease
- Vascular: post-hepatic portal HTN (right heart failure, Budd-Chiari syndrome, veno-occlusive disease)
- Other: infection (i.e., schistosomiasis), meds (e.g., MTX, isoniazid, amiodarone; see LiverTox), cryptogenic/idiopathic, carnitine/choline deficiencies

NATURAL HISTORY AND RISK STRATIFICATION (J Hepatol 2006;44:217)

- MELD Na score: predicts 90d mortality, used for transplant allocation using Na, Tbili, INR, Cr,
- New MELD 3.0 added: 1) female sex and albumin to correct transplant disparities for women, 2) interaction btwn Tbili & Na and albumin &Cr, 3) upper bound of Cr of 3 (Gastro 2021;161:1887)
- Child-Pugh class: assesses cirrhosis severity, predicts 1-2y mortality using Tbili, INR, albumin, presence of ascites encephalopathy
    - Compensated: Child-Pugh Class A; median survival 12y, 1y survival >95%. 5-10% risk of decompensation per year
    - Decompensated: Child-Pugh Class B/C; median survival 2y, 1y survival 40-80%

COMPLICATIONS OF CIRRHOSIS

- Portal hypertension: esophageal varices, portal hypertensive gastropathy, hypersplenism (→cytopenias), ascites, SBP, hepatorenal syndrome, hepatic hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension, cirrhotic cardiomyopathy
    - Hepatic venous pressure gradient (HPVG) is gold standard measurement for portal HTN (gradient b/w portal vein and IVC)
    - Normal HVPG <5mmHg; Portal HTN ≥6; Clinically-significant portal HTN: ≥10; Risk of EV bleed: ≥12
- Hepatic encephalopathy: see *ESLD: HE*
- Immune dysfunction: increased risk of infection; bacterial and fungal infections are major causes of morbidity & mortality
- Endocrinopathies: hypoglycemia, thyroid dysfunction, hypogonadism, hyperestrinism (palmar erythema, spider angiomata)
- Coagulopathy: see *ESLD: Hematologic Abnormalities*
- Portal vein thrombosis: ↑risk due unbalanced hemostasis & slowing of portal flow. Start AC for acute PVT w/ LMWH (unless high bleeding risk); transition to DOAC or warfarin once stable & continue at least 6mo (AGA: Gastro 2019;157:33)
- Hepatocellular carcinoma: see *ESLD: HCC*
- Frailty: encompasses sarcopenia, functional decline, deconditioning, malnutrition, impaired cognition. A/w decompensation, hospitalization, and mortality (Hepatology 2017;66:564; Am J Gastroenterol 2016;111:1759)

VIBES: a systematic approach to the management of cirrhosis

General: etiology of cirrhosis, complications, compensated/decompensated, etiology of decompensation (infection [including new/reactivation of HBV/HCV], GIB, EtOH, HCC, dehydration, meds, surgery, etc.), Child-Pugh class, MELD3.0 score

Volume (ascites, edema, hepatic hydrothorax, hepatorenal syndrome)

- Current diuretics & response; dietary Na^+ restriction (<2 g/d), fluid restriction 1.5L (if Na<125)
- Prior history of LVPs, thoracentesis for hepatic hydrothorax, consideration of TIPS if refractory

Infection

- Prior history of SBP, whether has indication for 1° or 2° ppx
- Current treatment or ppx

Bleeding (esophageal/gastric varices, portal hypertensive gastropathy, coagulopathy) (JOURNAL OF HEP 2022;76:959)

- Prior history/source of bleeding, therapies (e.g., banding, sclerotherapy, TIPS), current prophylaxis (β-blocker, carvedilol preferred)
- Current bleed: severity, IV access, H/H trends, medical therapy (PPI/octreotide), results/plan for EGD, SBP ppx as above

Encephalopathy

- Prior history, precipitant, and treatment
- Current severity, trend, precipitant, medicines, goal #BM (e.g., 4 BM/day, 500cc stool, mental status improvement)

Screening/Surgery (transplant)

- Vaccinations: HAV, HBV, Influenza, Pneumovax, Prevnar, COVID, all other standard vaccines, see Transplant ID
- Maintenance: alcohol abstinence, avoid NSAIDs, HCC screening with q6mo RUQUS ± AFP
- Transplant status: listed or not listed, MELD score, Milan criteria if HCC

ASCITES (AASLD: Hepatology 2021; 74(2):1014)

- Most common cirrhosis complication (50% in 10 years); development of ascites → 15% 1y mortality, 44% 5y mortality
- Pathophys: portal hypertension (>12 mmHg)→ ↑NO, prostaglandins, glucagon → splanchnic arterial vasodilation → ↓intravascular volume and SVR → ↑RAAS, ADH → Na & water retention. Severity of dilutional hypoNa (from ADH secretion) ∝ ↓ survival
- Diagnosis: Ultrasound to visualize. **Dx para** indicated for **ALL** patients with cirrhosis and ascites presenting to the hospital. No role for routine use of ppx FFP or platelets (Hepatology 2021;73:366). EARLY paracentesis (within 24 hours of admission) is associated with reduced inpatient mortality and 30-day readmissions (AJG 2019; 114:1863)
  - Studies: **cell count w/ diff, albumin, total protein, GS/Cx** ± glucose, LDH, amylase, TG, bilirubin, cytology, AFB Cx/ADA (TB)
  - DDx: **portal HTN** vs. non-portal HTN. **SAAG (serum ascites albumin gradient)** differentiates 97% of time (Annals 1992;117:215).

SAAG ≥1.1 g/dL: related to portal HTN	SAAG <1.1 g/dL: NOT related to portal HTN
Etiology related to portal hypertension	**Etiology not related to portal hypertension**
• Cirrhosis (ascites fluid total protein [AFTP] <2.5) • CHF, constrictive pericarditis (AFTP >2.5) • Acute hepatitis (including EtOH) • Acute liver failure • HCC, massive liver metastases Budd-Chiari syndrome (AFTP >2.5) • Portal vein thrombosis	• Infectious (Secondary bacterial peritonitis, Peritoneal TB) • Peritoneal carcinomatosis (+cytology) • Chylous ascites (triglycerides >200) • Hypoalbuminemia (nephrotic syndrome, protein-losing enteropathy, severe malnutrition; Ascitic fluid total protein <2.5) • Serositis (e.g., SLE) • Pancreaticobiliary (i.e., bile leak, disrupted pancreatic duct)

- Management of ascites:
  - **1st line:** <2g Na, ⃠EtOH, ⃠NSAIDs, diuretics (see below), avoid ACEi/ARB (↓renal perfusion), stop anti-hypertensives when MAP < 82 mmHg, fluid restrict 1L if Na <125
    - *Initiating therapy:* **100mg/d spironolactone + 40mg/d furosemide for starting dose (5:2 ratio).** Ideally single, daily AM dosing. Ratio maintains eukalemia & mobilizes fluid faster. Consider spironolactone alone for mild first ascites if outpt (lasix is added for normokalemia, never add it alone for managing ascites).
    - *Ongoing therapy:* ↑dose q3-5 days if inadequate diuresis (5:2 ratio, though can increase lasix PRN if hyperK). Max doses: 400mg spironolactone and 160mg furosemide. ∆ to eplerenone ($$) or amiloride if painful gynecomastia w/ spironolactone
    - Check U_{Na}/U_K ratio if pt gaining weight/requiring LVPs on diuretics; U_{Na}/U_K <1 suggests ineffective diuretic dose or resistance; U_{Na}/U_K >1 suggests >2g Na dietary intake
  - **Weight loss goals: 0.5 kg/d** (TBB -500) if no peripheral edema (AKI risk if too fast); if edema, 1 kg/d or -1L. **Avoid IV diuretics** (azotemia risk ↑). Ascites mobilizes fluid slower than other compartments at a rate of 0.5L/day (Gastro 1986;90:1827)
  - **Therapeutic LVP**: indicated for tense or refractory ascites or inability to use diuretics; **if >5L removed, give 6-8g albumin for every 1L ascites removed** to reduce risk of post-paracentesis circulatory dysfunction (PPCD); if >8L removed, risk of PPCD ↑
  - Unproven therapies: long-term administration of albumin (40g 1-2x weekly, $$) in pts with cirrhosis and uncomplicated ascites may offer survival benefit (Lancet 2018;391:2417) but no benefit (and potential harm) in hospitalized pts with acute decompensated cirrhosis targeting albumin > 3 g/dl (NEJM 2021; 384:808). SGLT2i may also ↓ ascites. (Hepatology 2020; 72(5):1880)
- Refractory ascites (10% of patients; associated with decreased survival):
  - Defined as: 1) unresponsive to Na-restriction & high-dose diuretics (or unable to tolerate iso HE, lytes, azotemia) or 2) rapid reaccumulation after LVP; associated with very advanced cirrhosis and low urinary excretion of Na
  - Mgmt: R/o PVT and HCC. D/c diuretics if U_{Na}<30mEq/day, discontinue βBs (↑mortality in refractory ascites [Hepatology 2010;52:1017]), midodrine TID (J Hepatol 2012;56:348), serial LVPs (<8L ~q2w), TIPS if intolerant of LVPs (poor TIPS candidate if: MELD>18, Child-Pugh class C cirrhosis, heart failure, severe HE), indwelling peritoneal catheters in certain cases (e.g., EOL)

SPONTANEOUS BACTERIAL PERITONITIS (SBP) (AASLD: Hepatology 2021; 74(2):1014)

- **Must r/o SBP in all inpatients w/ cirrhosis & ascites ASAP w/ dx para and blood Cx**; 10-30% hospitalized pts w/ cirrhosis have SBP. Look for abdominal pain, TTP, ileus, HE, and AKI as presenting sxs, but 1/3 of patients may be asx
- Diagnosis: **>250 PMN/L** w/ positive GS/Cx (SBP) or negative GS/Cx (CNNA = similar mortality to those w/ +Cx; treat similarly)
  - RBC >50,000/mm^3, often due to traumatic tap → correct PMN count by subtracting 1 PMN for every 250 RBCs
- Usually monomicrobial; GNR 70% (*E. coli*, *Klebsiella)*, GPC 25% (*S. pneumoniae*), anaerobes 5%; if polymicrobial, consider secondary bacterial peritonitis 2/2 perforation vs. loculated abscesses. Bowel perf. suggested if ≥2 of the following: TP >1, LDH >ULN, or Glc <50; also CEA >5 & ALP >240 (Runyon's criteria)
- Treatment:
  - **1) Abx: Community acquired: CTX 2g q24h x 5d;** IV cipro (400mg q12) if allergy to cephalosporin (unless taking cipro for ppx)
    - **Tx should be broader if risk of MDRO infxn** (recent hospitalization, nosocomial infxn, ICU pts): **Pip-Tazo + Daptomycin** (if prior VRE infxn or GI colonization) **OR Meropenem** if known MDR gram negative organisms or recent Pip-Tazo exposure
  - **2) 25% albumin:** 1.5g/kg day 1 + 1.0g/kg on day 3, max 100g (given risk of AKI in SBP) (Note: AASLD recommends for all pts *but some groups only recommend for those meeting study pop. criteria: Cr >1, BUN >30, or TBili >4* (NEJM 1999;341:403).
  - **Hold βBs** while hospitalized given increased risk of AKI & HRS once SBP is diagnosed, may attempt reintroduction with GI once recovered (Gastro 2014;146:1680).
  - Repeat diagnostic para 48 hours after starting abx to assess response. A negative response is defined by a ↓ in PMN count <25% from baseline → broaden abx and investigate secondary peritonitis w/ CTAP+GI consult. Repeat para may be avoided if an organism is isolated, it is susceptible to the abx used, and pt is improving clinically (not widely in practice yet at MGH)
- Prophylaxis:
  - **IV CTX 1g q24h x5 days if GIB**
  - All patients w/ prior SBP should receive 2° PPX (after full tx above) w/ **PO cipro 500 qd** (at MGH) or PO Bactrim DS qd
  - Consider 1° prophylaxis if ascitic TP <1.5 AND impaired renal function (Cr ≥1.2, BUN ≥25 or Na ≤130) or liver failure (Child score ≥9 and bilirubin ≥3) (Hepatology 2021;74(2):1014)

Gastroenterology

End Stage Liver Disease

HEPATIC ENCEPHALOPATHY (HE) (NEJM 2016;375:1660; AASLD: Hepatology 2014;60:715)

- Pathophysiology: ↑NH_3 → neurotoxic effects, abnl neurotransmission, ↑GABA- & BDZ-like neurotransmitters & altered glutaminergic inputs → ↓excitatory transmission. In ALF, acute ↑NH_3 → cerebral edema
- Diagnosis: clinical. Serum NH_3 should not be used to screen for HE. **↑NH_3 does not add diagnostic or prognostic value** in CLD (JHM 2017;12:659). Only helpful in ALF (predicts mortality). **Trend via exam findings** (see grades). Exclude other causes of AMS.
- Classification: type of underlying disease, severity grade, time course (episodic, recurrent, persistent), precipitations (precipitated vs non-precipitated)
- Asterixis: "flapping tremor" is **negative myoclonus** w/ loss of postural tone; elicit with hyperextension of wrists or squeezing of examiner's fingers (milk maids sign)
- Precipitants: infection, dehydration/overdiuresis, GIB, ↓K or alkalosis (↑renal NH3), renal failure, constipation, hypoxia, sedatives/BZD/opioids, new HCC, new clot, TIPS
- Treatment: ↓GI NH_3 absorption, avoid/correct precipitating factors
  - **Lactulose**: Δs gut microbiome → ↓pH → traps NH_4^+ in colon; has laxative effect; 30mL q2h until BM → titrate to 3-4 BM/day, often dosed 2-4x a day (PO or enema)
  - **Lactulose + rifaximin 550mg BID > lactulose alone** for HE reversal. Add rifaximin ($$) if refractory or 2nd admission
  - If refractory, consider non-standard therapies: oral branched-chain AAs (Cochrane Reviews 2017;5), IV L-ornithine L-aspartate (Hepatology 2018;67:700), probiotics (Cochrane Rev 2017;2), PEG (JAMA Int Med 2014;174:1727); FMT (Gastro 2019;156:1921)
  - Maintain K >4 to improve ammonia clearance via kidneys (Mineral electrolyte metab.1993;19:362)
  - Nutrition: calories: 35-40kcal/kg/day, protein 1.2-1.5g/kg/day (in general, don't restrict protein intake unless HE worsening)

Grades of Hepatic Encephalopathy (West Haven Criteria)		
Covert	1	Inattention, euphoria/ anxiety, **altered sleep pattern**, ↓attention span
Overt	2	Lethargy, time disorientation, **asterixis**, personality Δs, hypoactive DTRs
	3	**Somnolence**, responsive to stimuli, time & place disorientation, hyperactive DTRs
	4	**Coma,** unresponsive to pain

VARICEAL BLEEDING (AASLD: Hepatology 2024;79:1180)

- Clinically Significant Portal HTN (CSPH): HVGP ≥ 10 OR varices on EGD OR portosystemic collaterals/ascites on imaging OR liver stiffness (LSM)* by transient elastography ≥25 kPa, LSM 20–24.9 kPa w/ plt <150, or LSM 15–19.9 w/ plt <110.
  *Caution: Careful interpretation in obesity, metAFLD, ALT > 3xULN, and PSC. PPV of test drops.
- EGD screening: esophageal varices most common. If alt. evidence of CSPH and on NSβB, sEGD may be deferred. Pursue sEGD if unclear LSM w/o surrogate of PH on images and C.I. to empiric NSβB, continue q2yr if ongoing liver injury or q3yr if quiescent. If known varices or decomp cirrhosis and C.I. to NSβB, sEGD q1yr. Avoid sEGD if LSM<20 & plt>150, as high risk varices unlikely

1° PPX	**Compensated cirrhosis without CSPH**: No 1° PPX indicated. Check LSM every 3-5y if LSM5-9.9kPa or annually if 10-14.9kPa. **Compensated cirrhosis with CSPH** or **decompensated cirrhosis w/ only ascites**: Carvedilol (6.25mg qd x3d → ↑ to 6.25mg BID) C.I. in asthma, AV block, SSS, HR <50 **Decompensated cirrhosis:** Non-selective βB (NSβB, see below) are technically tx of choice, however MGH favors continuing carvedilol if tolerated. Indications to stop βB outside of acute illness are most often 1) BP is unable to tolerate 2) recurrent AKI (esp. iso necessary diuretics) **If known EV and C.I. to NSβB:** Serial endoscopic variceal ligation (EVL) q2-8w until eradication in med/large EV with screening q1-2yrs	
2° PPX	Episode of variceal bleeding without placement of TIPS → **ppx to prevent recurrence** w/ combination of non-selective βB + EVL	- **Non-selective βB**: *nadolol* 20-40mg qd or *propranolol* 20-40mg BID on day 5 s/p bleed (d/c of vasoactives); adjust every 2-3d to goal HR 55-60, SBP>90; max daily dose in pts with|without ascites: propranolol 160|320mg/d or nadolol 80|160mg/d - **Serial EVL**: q1-4w until obliteration; repeat EGD 3-6mo after & then q6-12mo

- **Acute bleeding**: Assess airway and IV access. IV PPI, IV octreotide (50 mcg bolus followed by 50 mcg/hr for 2-5 days), CTX 1g q24h x 5d, EGD within 12hrs. Resuscitate w/ IVF/pRBCs prior to intubation and give erythromycin for EVL. Balloon tamponade as a bridge (GI), urgent TIPS (IR) if cannot band. Conservative transfusion: goal Hgb 7 (NEJM 2013;368:11), avoid attempts to correct INR/plts. Start enteral nutrition w/ control of bleeding and assess for provoking factor (i.e. PVT, HCC, etc). See *Upper GI Bleeding*
- **Indications for TIPS**: early "preemptive" TIPS (<72h) in pts with high risk of treatment failure or rebleeding (Hepatology 2024;79e224); "rescue" TIPS if uncontrolled bleeding or if recurs despite max medical & endoscopic therapy
- Gastric varices: similar mgmt. of acute bleed but difficult to band. Consider TIPS (favored if EV too), BRTO, or endoscopic glue/coil

HEMATOLOGIC ABNORMALITIES (AGA: Gastro 2019;157:33; NEJM 2011;365:147; CGH 2013;11:1064; Thromb Haemost 2018;118:1491)

- Cytopenias: **thrombocytopenia** (splenomegaly, ↓TPO), **leukopenia** (splenomegaly), **anemia** (bleeding, hemolysis) may have BM suppression from EtOH/infection, nutritional deficiencies (e.g. folate), direct effect of HCV/HBV
- Coagulation abnormalities: **↓coagulation factors** (except for FVIII), **↓anticoagulant proteins** (C, S, ATIII), **dysfibrinogenemia**, **accelerated fibrinolysis** (↑tPA), +/- ↓ Vit K→ **↑risk of both clotting and bleeding** & patients **not** auto-anticoagulated; balance tends to favor thrombosis in early stages vs bleeding in late stages of cirrhosis
  - **Labs**: ↑PT/INR, ↑PTT, ↑/nml fibrinogen (though does not function normally; ↓ if fulminant), ↑/nml D-dimer (vs ↑↑ in DIC), ↑factor VIII (vs ↓ in DIC); note PTT and PT/INR do **NOT** correlate with risk of bleeding or clotting
- **Anticoagulation** (J Hepatol 2017;66:1313; JACC 2018;71:2162):
  - VTE ppx: should not be withheld unless high risk of bleeding or plts<50
  - Systemic AC: ok unless Child-Pugh C or↑ bleeding risk. EGD if EVs prior. VKA, LMWH, or DOAC all options. VKA dosing c/b ↑baseline PT/INR; LMWH c/b ↓ATIII levels; some DOACs safe (apixaban preferred)– can use w/ caution in Child-Pugh B
- **Bleeding**: consider role of coagulation factor deficiency, dysfibrinogenemia, hyperfibrinolysis, thrombocytopenia
  - If suspect vitamin K deficiency, give **vitamin K** 10mg x3d to correct nutritional component
  - **pRBCs** Hgb <7, **platelets** <50k, **cryo** for fibrinogen <100-120. FFP if persistent (though large volume → ↑portal pressures)
  - Delayed bleeding or oozing from mucocutaneous sites → **Amicar** (3g PO QID or 4-5g IV over 1h → 1g/h) or TXA (1g IV q6h)
- **Procedures**:
  - Platelets: >50k for surgery, TIPS, liver biopsy, or other procedure w/ high bleeding risk; TPO agonists are not generally recommended but in specific instances can reduce need for peri-procedural PLT transfusions (but takes ~10d to ↑PLT) (NEJM 2012;367:716; Gastro 2018;155:705). **No** role for plt transfusion for routine paracentesis (data ok with plt >19k).
  - PT/INR: **NO** benefit to giving FFP pre-procedure to "correct" INR. ↑volume can ↑bleeding risk by ↑portal pressures

HEPATOCELLULAR CARCINOMA (HCC) (AASLD: Hepatology 2023;78:1922)

- 2-4% risk per year. May be asx, lead to decompensation, and/or have sx related to mass effect (pain, early satiety, palpable mass)
- 1° prevention: HBV vax in high-risk pts not vaccinated at birth, HBV/HCV antiviral tx, healthy lifestyle, coffee consumption (1+ cup)
- Screening indicated in:
  - **Cirrhosis due to *any* etiology**, except in Child-Pugh Class C pts not on transplant list (due to low survival time)
  - Chronic HBV w/o cirrhosis if: M >40 / F >50 from endemic ctry, African/African-American >30, FHx HCC, or PAGE-B score ≥10
- Screen with: **RUQUS ± AFP q6mo**; if U/S visualization is limited (e.g., ascites), can use multiphase CT or contrast-enhanced MRI
  - If lesion <1cm, repeat US + AFP in 3-6mo
  - If lesion ≥1cm, AFP ≥20ng/mL, or rising AFP, obtain multiphase CT or MRI & proceed according to LI-RADS class
- Staging:
  - Barcelona (BCLC) system: size, # of nodules, LN & portal vein involvement, mets, Child-Pugh score, performance status
  - Recommended discussion at multidisciplinary tumor board; if HCC > BCLC Stage 0, obtain noncontrast CT chest for eval of mets
- Management:
  - *Curative*: surgical resection (1st line if Child-Pugh A & T1-T2 nodule) ± adjuv ICI, OLT (if non-resectable but within Milan criteria)
  - *Noncurative*: ablation, chemoembolization (TACE), radioembolization (TARE), radiation, chemo, immunotherapy
  - Within Milan criteria → locoregional tx (LRT) as bridge to OLT. Outside Milan → LRT to downstage to w/in Milan → OLT
  - Not OLT candidate (and non-resectable) → LRT and/or systemic chemotherapy
- Prognosis: survival by BCLC stage: *0-A (early)*: >5y, *B (intermediate)*: >2.5y, *C (advanced)*: >2y, *D (terminal)*: 3mo

HEPATIC HYDROTHORAX (AASLD: Hepatology 2013;57:1651, Hepatology 2020;72:1851)

- ~5-15% pts w/ cirrhosis. Transudative effusion due to **ascites → pleural space** (neg. intrathoracic pressure) via small diaphragmatic defects. Can be seen w/o significant ascites. **Unilateral**: R- (~75%) > L-sided (~15%) > bilateral (~10%) (Medicine 2014;93:135)
- Diagnosis: exclude other causes of transudative effusion; thora + imaging (chest CT, abd U/S, TTE); radioisotope inj. if dx unclear
- Treatment: first line: **diuretics, 2g Na restriction**. Therapeutic thora for dyspnea. Serial thoras, TIPS, pleurodesis, surg. repair or OLT if refractory. **Chest tube not recommended due to risk of serious complications + ↑ mortality 2.5%** (Chest 2019;155:546)
- **Spontaneous bacterial empyema**: can become infected (~15%) due to translocation of bacteria from abd. cavity. ~40% occur in absence of SBP (Hepatology 1996;23:719). Dx: >250 PMNs w/ +Cx or >500 PMNs w/o +Cx. No e/o PNA. Tx: same as for SBP

HEPATOPULMONARY SYNDROME (HPS) (NEJM 2008;358:2378; EASL: J Hepatol 2018;69:406; ILTS: Transplantation 2016;100:1440)

- V/Q mismatch (shunt) + O_2 diffusion limitation **via intrapulmonary vascular dilatations**; mechanism unclear, **possibly ↑ NO**
- Presentation: shunting tends to occur at bases → **platypnea** (dyspnea when upright, relieved when supine) & **orthodeoxia** (upright hypoxemia, PaO_2 ↓ by 4 mmHg or ≥3-5%), clubbing, cyanosis, diffuse telangiectasias, hypoxemia (PaO2 <70-80)
- Diagnosis: If SpO_2 <96% →↑A-a gradient ≥15mmHg (or ≥20mmHg if age ≥65) or PaO_2 <80mmHg → **TTE with late bubbles** (3-6 cardiac cycles after RA vs early bubbles in PFO) → PaO_2 to grade severity
  - ^{99m}Tc MAA scan is alternative to TTE but more invasive, less sensitive. May be useful in quantifying shunting if severe hypoxemia and coexisting intrinsic lung disease
  - Pulmonary angiography performed if severe hypoxemia poorly responsive to 100% O2 & areas amenable to embolization
  - PFTs can be performed to evaluate for intrinsic lung disease; ↓DLCO in HPS
- Management: no effective medical therapies. Monitoring q6-12mo in mild to moderate HPS. Consider OLT in pts w/ severe/very severe HPS (PaO2 <60); OLT can significantly improve (and reverse) HPS – MELD exception points given for severe HPS

PORTOPULMONARY HYPERTENSION (EASL: J Hepatol 2018;69:406; ILTS: Transplantation 2016;100:1440)

- Rare cause of **group 1 pulmonary hypertension** in setting of portal HTN; 3x risk in F > M; ↑ risk in autoimmune liver disease
- Pathogenesis: ↓blood flow to pulm. arterial bed. Mechanisms unclear but include vasoconstrictors normally cleared by liver (e.g., endothelin-1, estradiol) reaching pulmonary circulation, ↓prostacyclin synthase, endothelial proliferation and PLT aggregation
- Diagnosis: screening w/ TTE (PASP >30mmHg; 100% NPV); confirmation is euvolemic RHC w/ PAH (mPAP ≥20mmHg, PCWP <15 mmHg, PVR >3) in pt with portal HTN in absence of other etiology (*mild*: mPAP 25-35, *moderate*: mPAP 35-44, *severe*: mPAP ≥45)
- Management: may benefit from advanced therapies (epoprostenol, bosentan, sildenafil, iloprost); OLT can improve PAH (MELD exception points given for moderate PPHT); β-blockers and TIPS may be harmful and should be avoided
- Transplant: increased risk of morbidity/mortality with mPAP ≥35; mPAP ≥50 is a contraindication to transplant

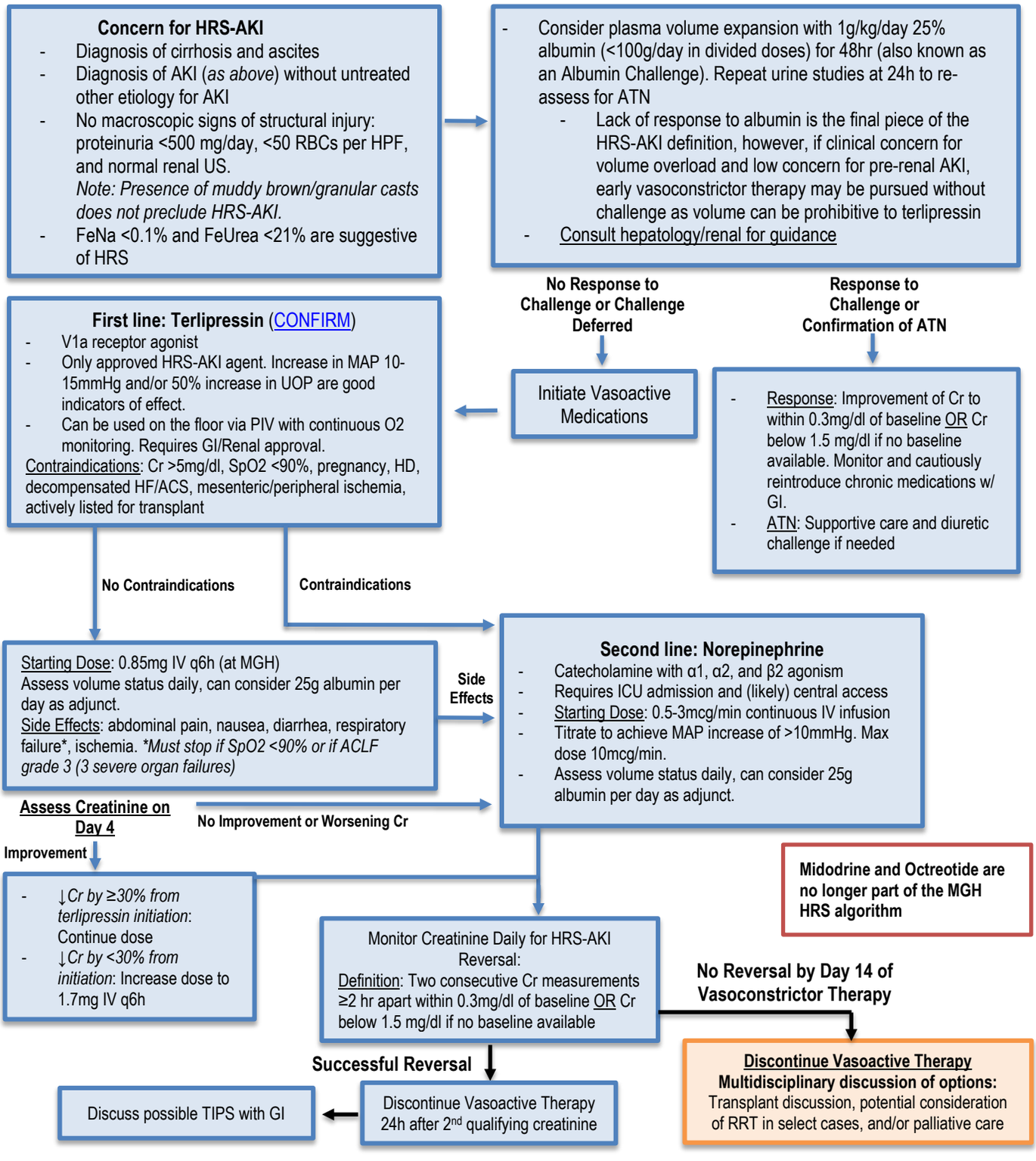
CIRRHOTIC CARDIOMYOPATHY (Hepatology 2020;71:334; EASL: J Hepatol 2018;69:406, JACC 2010;56:539)

- Chronic cardiac dysfunction in cirrhosis pts w/o known cardiac disease; characterized by 1) impaired cardiac contractility in response to stress, 2) altered diastolic relaxation, 3) electrophysiological abnormalities such as prolonged QTc and chronotropic incompetence
- Pathophysiology: myocardial dysfunction 2/2 systemic inflammation; shear stress from portal hypertension → mechanical force on myocardial fibers; other possible mechanisms involve collagen configuration, sodium retention, activation of RAAS, ↑ bile acids (*Biochim. Biophys.* 2018; 1864:1345)
- Prevalence: up to 50% of pts undergoing liver transplantation have signs of cardiac dysfunction
- Diagnosis & Treatment: echocardiography (CCC Criteria) w/ dynamic stress testing; OLT and HF management as in pts w/o cirrhosis
- Prognosis: largely subclinical; risk with stressors (infection, paracentesis, TIPS, OLT); detailed cardiac assessment before intervention

HEPATORENAL SYNDROME (HRS) (Clin Gastro Hep 2018;16:162; BMJ 2020;370:2687, NEJM 2023;388(8)e733, Gastro 2024;166:202)

- Pathophysiology: portal HTN → ↑NO, prostaglandins → splanchnic vasodil. → ↓EABV → ↑RAAS, ADH, SNS → renal vasoconstr.
- Diagnosis: ***dx of exclusion***; need: (1) advanced hepatic failure w/ portal HTN (ascites)
  (2) AKI: ↑sCr > 0.3 mg/dl from baseline within 48 hrs OR ↑sCr >1.5x baseline within past 7d OR UOP <0.5 ml/kg/hr x6hrs
  (3) absence of and/or optimization of alternative AKI etiology. Examples: shock (GIB, sepsis, pancreatitis), infection (SBP), dehydration (diuretics/diarrhea), nephrotoxin (ATN: IV contrast, bile cast nephropathy. AIN: Abx, NSAIDs, PPI), obstruction, glomerular disease (e.g. IgA, MPGN, cryoglobulinemia).
- Type I (HRS-AKI): ↑Cr >2x b/l and >2.5 mg/dL in <2w; Type II (diuretic-resistant ascites): ↑Cr from 1.5-2.5mg/dl, slower progression
- Most Common HRS Precipitants: infection (SBP > other), GI bleed, fluid shifts after LVP, alcohol-related hepatitis
- Prevention: In SBP, albumin day 1 + day 3 has mortality benefit (Clin Gastro Hep 2013;11:123); 1° SBP ppx (Gastro 2007;133:818)
- Management: Obtain history and treat reversible causes. Discontinue diuretics, βB, ACEI/ARB, or other vasodilators or nephrotoxins. Obtain paracentesis for SBP eval. Obtain urine studies for urine sediment, FeNa, FeUrea, and renal ultrasound. Then see algorithm.

MGH Algorithm for the Diagnosis and Treatment of Hepatorenal Syndrome


Concern for HRS-AKI
- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI (as above) without untreated other etiology for AKI
- No macroscopic signs of structural injury: proteinuria <500 mg/day, <50 RBCs per HPF, and normal renal US.
Note: Presence of muddy brown/granular casts does not preclude HRS-AKI.
- FeNa <0.1% and FeUrea <21% are suggestive of HRS
- Consider plasma volume expansion with 1g/kg/day 25% albumin (<100g/day in divided doses) for 48hr (also known as an Albumin Challenge). Repeat urine studies at 24h to re-assess for ATN
- Lack of response to albumin is the final piece of the HRS-AKI definition, however, if clinical concern for volume overload and low concern for pre-renal AKI, early vasoconstrictor therapy may be pursued without challenge as volume can be prohibitive to terlipressin
- Consult hepatology/renal for guidance
No Response to Challenge or Challenge Deferred
Response to Challenge or Confirmation of ATN
First line: Terlipressin (CONFIRM)
- V1a receptor agonist
- Only approved HRS-AKI agent. Increase in MAP 10-15mmHg and/or 50% increase in UOP are good indicators of effect.
- Can be used on the floor via PIV with continuous O2 monitoring. Requires GI/Renal approval.
Contraindications: Cr >5mg/dl, SpO2 <90%, pregnancy, HD, decompensated HF/ACS, mesenteric/peripheral ischemia, actively listed for transplant
Initiate Vasoactive Medications
- Response: Improvement of Cr to within 0.3mg/dl of baseline OR Cr below 1.5 mg/dl if no baseline available. Monitor and cautiously reintroduce chronic medications w/ GI.
- ATN: Supportive care and diuretic challenge if needed
No Contraindications
Contraindications
Starting Dose: 0.85mg IV q6h (at MGH)
Assess volume status daily, can consider 25g albumin per day as adjunct.
Side Effects: abdominal pain, nausea, diarrhea, respiratory failure*, ischemia. *Must stop if SpO2 <90% or if ACLF grade 3 (3 severe organ failures)
Side Effects
Second line: Norepinephrine
- Catecholamine with α1, α2, and β2 agonism
- Requires ICU admission and (likely) central access
- Starting Dose: 0.5-3mcg/min continuous IV infusion
- Titrate to achieve MAP increase of >10mmHg. Max dose 10mcg/min.
- Assess volume status daily, can consider 25g albumin per day as adjunct.
Assess Creatinine on Day 4
No Improvement or Worsening Cr
Improvement
- ↓Cr by ≥30% from terlipressin initiation: Continue dose
- ↓Cr by <30% from initiation: Increase dose to 1.7mg IV q6h
Midodrine and Octreotide are no longer part of the MGH HRS algorithm
Monitor Creatinine Daily for HRS-AKI Reversal:
Definition: Two consecutive Cr measurements ≥2 hr apart within 0.3mg/dl of baseline OR Cr below 1.5 mg/dl if no baseline available
No Reversal by Day 14 of Vasoconstrictor Therapy
Successful Reversal
Discontinue Vasoactive Therapy
Multidisciplinary discussion of options:
Transplant discussion, potential consideration of RRT in select cases, and/or palliative care
Discontinue Vasoactive Therapy 24h after 2nd qualifying creatinine
Discuss possible TIPS with GI

Gastroenterology

Liver Transplant

Indications for Liver Transplant (AASLD: Hepatology 2014;59:1144)

Milan Criteria:
One lesion ≤5cm or up to 3 lesions all ≤3cm
No extra-hepatic involvement
No major vessel involvement

- Acute liver failure: see *Acute Liver Injury & Failure*
- Cirrhosis with MELD ≥15 or complication (e.g., ascites, HE, EV bleed, HRS, chronic gastropathy bleed). (AJT 2005;5:307) Child B cirrhosis w/ portal HTN and low MELD can be considered also. Start/refer for evaluation at MELD >10 (to give time for education/evaluation).
- HCC: *first-line option* within Milan criteria but unsuitable for resection (NEJM 1996;334:693; Hepatology 2018;69:182) assigned score of 22; can be "down-staged" to within Milan with treatment; composite criteria (surrogates of tumor biology such as AFP, treatment response, tumor size, number of nodules) may replace conventional criteria. See *ESLD: HCC*
- Liver-based metabolic disorders w/ systemic manifestations: A1AT deficiency, familial amyloidosis, Wilson's disease (won't resolve neurologic issues), hemochromatosis, glycogen storage disease, primary oxaluria
- Decompensated biliary disorders: PBC (intractable pruritus), PSC (recurrent cholangitis and sepsis)
- Systemic complications of chronic liver disease: hepatopulmonary syndrome, portopulmonary HTN
- Conditions qualifying for Exception Points (see below under "Prioritization for Liver Transplant")

Contraindications to Liver Transplant

- Absolute: severe cardiac or pulmonary disease, AIDS, HCC w/ metastatic spread, ongoing EtOH/illicit substance use within 6mo (changing for EtOH in select cases; see *Alcohol-Related Liver Disease*), uncontrolled sepsis, anatomic abnormality that precludes LT, intrahepatic cholangiocarcinoma, extrahepatic malignancy (other than skin, not meeting criteria for cure), mPAP >35 or PVR >400, fulminant hepatic failure with sustained ICP >50mmHg or CPP <40mmHg, hemangiosarcoma, persistent nonadherence to medical care, lack of adequate social support system
- Relative: BMI ≥40, HIV (all center-specific); age >70 is not a contraindication (Mayo Clinic Proceedings 2009; 84)

Prioritization for Liver Transplant

- Prioritized based on MELD Score (AJT 2015;15:2552)& stratified by blood type
- Certain conditions result in impaired survival but are not directly accounted for in the MELD score → specific disease-related criteria for MELD exceptions that upgrade MELD score w/ subsequent automatic upgrade q6mo
- *Standard MELD exceptions:* HCC (w/in Milan criteria, AFP <1000), hepatopulmonary syndrome (RA PaO2 <60mmHg), portopulmonary HTN (mPAP <35), familial amyloid polyneuropathy (TTR mutation), primary hyperoxaluria, CF (FEV1 <40%), hilar/early-stage cholangiocarcinoma, hepatic artery thrombosis (w/in 14d of LT but not meeting status 1A criteria), cystic fibrosis
- Can also petition review board for non-standard exceptions (e.g., refractory complications) esp if MELD score does not reflect severity of mortality/morbidity related to the liver disease
- Some patients are candidates for double transplantation (e.g. with heart, kidney, lung)

Transplant Evaluation Process

- Laboratory testing: order set in EPIC; BMP, Ca, Mg, Phos, LFTs, GGT, CBC w/ diff, PT/PTT, T&S, Fe/TIBC, ferritin, ceruloplasmin, A1AT level, autoimmune (ANA, ASMA, AMA, SPEP), viral hepatitis (HAV IgG, HBsAg, HBsAb, HBcAb [total], HBeAb, HBV DNA, HCV Ab & PCR, HDV Ab), HIV, EBV, CMV, VZV, HSV, RPR, toxo, measles/mumps/rubella titers, IGRA, AFP, PSA, amylase, uric acid, total cholesterol, U/A, UCx
- Additional tests: ABG (on RA), EKG, CXR, U/S w/ Doppler, abdominal CT or MRI (eval for HCC), age-appropriate cancer screening (colonoscopy annual for PSC w/ IBD, mammogram, pap smear), bone density, cardiopulmonary eval as below
- Immunizations: HAV, HBV, pneumococcus, influenza, Tdap, MMR, varicella, COVID19
- Consults: Hepatology; will subsequently involve transplant surgery, transplant psychiatry, social work (address psychosocial issues, adequacy of support, financial screening, insurance counseling), nutrition, transplant ID if indicated
- Cardiopulmonary eval: TTE w/ bubble ± PFTs. Dobutamine stress echo may be indicated (typically if >40 or CAD RFs). Optimal strategy debated – AASLD: stress testing in all candidates; AHA/ACC: if multiple CAD RFs (JACC 2012;60:434); may consider PCI prior to LT if significant stenosis; if concerned for HPS can get Tc99 shunt scan
- ID eval: eval for LTBI as above and tx pre-LT if able. Coccidiomycosis, strongyloides testing if from endemic area. Dental extractions pre-LT. HIV not a contraindication if immune function adequate. HBV tx pre-LT. HCV can be tx pre- or post-LT (timing depends on if LT imminent, access to HCV+ donor, comorbidities). Transplant ID consult
- Combined kidney transplant: eligible if CKD w/ GFR ≤30 or ESRD on HD; sustained AKI w/ dialysis ≥6wk or GFR ≤25 for ≥6wk; or metabolic disease (e.g. hyperoxaluria) (UNOS/OPTN: AJT 2016;16:758)
- Living Donor Transplant (LDLT): recipients should fulfill same minimal listing criteria as for deceased donor. Recipients of LDLT have reduced wait list mortality compared to potential recipients of deceased donor organs.

Nephrology

Acute Kidney Injury

DEFINING AKI (KDIGO 2012 Guidelines)

Stage	Serum Creatinine	Urine Output	Work-up and management
1	↑ **≥0.3 mg/dl** w/in 48h or ↑**1.5-1.9x** baseline w/in last 7d	<0.5 ml/kg/h for ≥6h	(1) H&P (2) monitor Cr and UOP (3) UA and sediment (4) urine electrolytes (5) renal U/S and other tests (below)
2	↑**2-2.9x** baseline	<0.5 ml/kg/h for ≥12h	Above measures plus: (1) renally dose meds (2) eval need for RRT (3) consider ICU for CRRT, pressors for renal perfusion (4) avoid subclavian CVCs/PICC (to preserve potential fistula sites) and RIJ CVC in case emergent HD need arises
3	↑**3x** baseline, Cr ≥4, ↓eGFR to <35 (<18 yo), or RRT	<0.3 ml/kg/h for ≥24h or anuria ≥12h	

Diagnostic Tips

- Serum Cr approximates GFR at steady state only (unable to estimate GFR w/ ΔCr): **must assume GFR <10 if ΔCr > 1 mg/dL/day**
- Drugs can impair Cr excretion without ΔGFR (BUN remains stable): trimethoprim (in Bactrim), H2 blockers (cimetidine), dronaderone
- ↑BUN out of proportion to Cr: pre/post-renal, UGIB, steroids. ↑Cr out of proportion to BUN: rhabdo, AIN, TMP-SMX, vanc, ↓ nutrition

STEPWISE WORKUP

1) History/exam: vitals (HTN/HoTN), volume status, exposures (contrast, meds), recent infection (IgA nephropathy 1-2d, post-strep GN in 10-14d), active infection (sepsis can induce ATN independent of BP or ↓RBF (JASN 2011;22:999)), trauma/myalgias/found down (rhabdomyolysis), rashes (AIN, vasculitis)

2) Urinalysis (UA): see *Urinalysis*. If AKI and UA demonstrate unexplained heme and protein, need to consider GN and renal c/s.

3) Urine chemistries:

- FENa: FENa <1% c/w pre-renal AKI, >2% c/w ATN. **ONLY** verified in **oliguric** AKI, not useful if on diuretics (FEUrea). Interpret with caution in baseline CKD or chronic prerenal disease (CHF/cirrhosis). Note: GN, rhabdo, & IV contrast can all cause FENa <1%. **Overall limited use**, except to rule out HRS with ↑FeNa (J Hosp Med 2016;11:77)
- FEUrea: if on diuretics and high pretest prob. of pre-renal physiology. FEUrea <35% c/w with pre-renal (Kid Int 2002;62:2223)
- Urine Osm: >500 is consistent with a pre-renal etiology (high ADH state)
- Urine protein: if proteinuria on UA, send serum albumin, urine total protein, urine microalbumin, & urine Cr. Urine albumin/protein ratio (APR) >0.4 suggests glomerular > tubulointerstitial process (Sn 88%, Sp 99%) (Nephro Dial Trans 2012;27:1534). Note: dipstick detects albumin, will not help identify light chains/paraprotein.

4) Urine sediment: see *Urinalysis*. Look for casts, RBC morphology.

5) Eosinophilia/eosinophiluria: Not recommended - poor test for AIN. Urine eos >1% has Sn 31%, Sp 68% (J Hosp Med 2017;12:343)

6) Renal U/S: exclude hydronephrosis; often preceded by bedside bladder ultrasound. In absence of a suggestive history, <1% of renal U/S for AKI showed post-renal etiology; can provide evidence of chronic processes if no known hx (BMC Nephrol 2013;14:188)

7) Monitor Cr, UOP, BP, and electrolytes: assess response to empiric treatment of presumed cause

8) Next if sediment or history suggests glomerular disease, broaden workup with C3/4, ANCA, anti-GBM, ANA, anti-dsDNA, HBV/HCV/HIV, cryo, SPEP/UPEP/SFLC as per below. Consider biopsy if expected to change treatment.

DIFFERENTIAL DIAGNOSIS OF AKI

PRE-RENAL	INTRINSIC			POST-RENAL
	GLOMERULAR	TUBULO-INTERSTITIAL	VASCULAR	
↓ Absolute volume - Bleeding - GI or skin loss - Diuretics - Osmotic diuresis - Cerebral salt wasting **↓ Effective volume** - CHF/cardiorenal - Cirrhosis/hepatorenal - Nephrotic syndrome - Sepsis/third-spacing **Δ renal dynamics** - NSAIDs/COX-2s - ACEi/ARBs - Abd compart. syndr. **Relative hypotension**	**Anti-GBM** **ANCA +** - Microscopic polyangitis - Granulomatosis with polyangiitis (GPA) - Eosinophilic GPA - Drug-induced ANCA **Immune complex** *Low complement:* - PSGN, SLE, cryo, MPGN, MGRS *Normal complement:* - IgA nephropathy/HSP - Fibrillary, immunotactoid	**ATN** - Ischemia, sepsis, toxic - Contrast, rhabdo, aminoglycosides **AIN** 1) Meds (see below) 2) Infectious: CMV, leptospirosis, legionella 3) Autoimmune/infiltrative: TINU, IgG4 disease, sarcoid, Sjogren **Crystals** - TLS (uric acid), acyclovir, sulfa abx, MTX, cipro, ethylene glycol, oxalate, bile acids **Proteins** - MM, amyloid, Ig deposition	**Microvascular** - TTP/HUS - APLAS - HELLP/eclampsia - Scleroderma - Meds (calcineurin inhibitor/CIN, gemcitabine) **Macrovascular** - RAS (athero, FMD) - Dissection - Renal artery/vein thrombosis - Polyarteritis nodosa	**Urinary retention** - BPH, meds, neurogenic - Foley dysfunction **Urinary obstruction** (bilateral) - Stones (single kidney/transplant) - Malignancy - Retroperitoneal fibrosis (Radiation) - IgG4 disease w/ retroperitoneal fibrosis - Congenital anomalies

Common nephrotoxins (not comprehensive): see AAFP (Am Fam Phy 2008;7:743) or StatPearls for list of common nephrotoxins
AIN: NSAIDs, β-lactams, ciprofloxacin, sulfa drugs, rifampin, PPIs (delayed effect), mesalamine, allopurinol, NSAIDs
Direct tubular injury: calcineurin inhibitors, ACEi/ARB, NSAIDs, TMP-SMX, MTX, acyclovir (IV>PO), protease inhibitors, amphotericin, tenofovir (proximal tubule), vancomycin (esp. with pip-tazo) (CID 2017;64:116), numerous cytotoxic, targeted, & immunotherapy cancer rx

MANAGEMENT

"A Euvolemic Kidney is a Happy Kidney; Fluids are NOT always the answer"

1. **Optimize hemodynamics, avoid nephrotoxins**: correct volume status – IVF and hold diuretics if hypovolemic, diuretics if hypervolemic. Stop NSAIDs/ACEi/ARBs. Avoid ↑glucose and contrast. No evidence of benefit for empiric diuretics in oliguria (JAMA 2002;288:2547). If large volume resuscitation or critically ill, generally LR > NS (NEJM 2018;378:819; NEJM 2018;378:829)
2. **Renally dose meds**: use Lexicomp for help dosing by GFR (note: GFR calculation assumes a steady state. Assess trajectory of AKI, if creatinine is rising, assume clearance is lower than GFR. If anuric, assume GFR is 0). Run MAR w/ pharmacy for additional support
3. **Manage complications**:
   - HyperK: check EKG, monitor on telemetry until improved. Can stabilize with calcium gluconate, shift K+ with insulin/dextrose, IVF/Lasix → Remove K from body with sodium zirconium cyclosilicate (lokelma), bowel reg, furosemide. Start low K diet.
   - HyperPhos: start phosphorus binder such as sevelamer (start >5.5 mg/dl) vs. calcium acetate depending on calcium level. **Avoid** IV calcium if Ca/Phos product> 70) as can precipitate. Low phos diet.
   - Metabolic acidosis: sodium bicarb PO/IV (see *Acid-Base Disorders*)
   - Bleeding with concern for uremic platelets: DDAVP 0.3 mcg/kg IV, onset 1h, lasts 4-8h
4. **Indications for HD (AEIOU)**: **A**cidosis (esp. pH <7.0, refractory to bicarb), **E**lectrolytes (refractory hyperK+), **I**ntoxication (lithium, ethylene glycol, metformin, salicylates, theophylline), refractory Volume **O**verload, **U**remia (encephalopathy, neuropathy, pericarditis)

RENAL EMERGENCIES (WHEN TO PAGE THE RENAL FELLOW OVERNIGHT)

- **Acidosis**: severe metabolic acidosis (pH <7.1, <7.2 w/ severe AKI) w/o rapidly reversible cause (i.e. DKA). Temporize with bicarb pushes and isotonic bicarb gtt, intubate and hyperventilate if unable to compensate by breathing off CO2. May need RRT particularly if other indications. *CVVH impact on lactic acid clearance is debated, pH correction is similar in correction rate to bicarbonate infusion.*
- **Hyperkalemia**: hyperK w/ ECG changes/arrhythmia or K >6.5 (>5.5 if rising from ongoing rhabdo/GI bleeding). Temporize with Ca gluconate, diuretics, insulin/D50, albuterol, etc. Note iHD clears K faster than CVVH so is preferred in stable pts who can tolerate iHD.
- **Hyponatremia**: call if severely symptomatic (AMS with low GCS, seizures, etc.) requiring bolus hypertonic saline +/- DDAVP clamp.
- **Anuria w/ ADHF**: place Foley, monitor UOP/MvO2/signs of shock (LFTs, Cr, Lactate, CI). Improving cardiac output (volume optimization with diuretics or HD, ± inotropes) will raise GFR.
- **Ingestions**: lithium, ethylene glycol, methanol (elevated osmolar gap -> elevated anion gap), metformin with end organ damage (i.e. renal failure, vision loss), see "Indications for HD (AEIOU)" above.
- **RPGN**: when suspected, urgent renal consultation to consider pulse dose steroids ± plasmapheresis. See *Glomerular Disease.*
- **Scleroderma renal crisis**: ACEi (captopril) at maximum tolerated dose (starting at 6.25 or 12.5mg, titrating up q4h). Avoid steroids.

SPECIFIC MANAGEMENT BY CAUSE

- **Acute interstitial nephritis (AIN)**: stop offending agent, consider prednisone 40-60mg qd for 1-2w if biopsy-confirmed or high pre-test probability though not great evidence (CJASN 2018;13:1851)
- **Cardiorenal syndrome (type 1)**: (Nat Rev Neph 2013;9:99; Circ 2019;139:e840)
  - Definition: 5 phenotypes that impact the heart and kidneys with various causal relationships. Type 1 is HF resulting in AKI.
  - Pathophysiology: decreased renal perfusion from ↑venous congestion ± ↓CO leads to a low trans-renal perfusion pressure. More of a problem with "under-draining" (congestion) than "under-filling" (perfusion)
  - Treatment**:** relief of renal venous congestion. Trend Cr against TBB and daily weights to test hypothesis, expect a lag effect.
    - Loop diuretics are first line for type 1 ± addition of thiazide (metolazone/chlorothiazide), see *Advanced Diuresis*
    - No benefit of low dose dopamine or nesiritide to improve forward flow (JAMA 2013;310:2533)
  - Ultrafiltration showed similar outcomes re: weight loss and CHF sx, but worsened renal function compared to pharmacologic therapy with loop/thiazide diuretics (NEJM 2012;367:2296)
- **Contrast-Induced AKI (CI-AKI, formerly "contrast-induced nephropathy")** (Nat Rev Nephrol 2017;13:169)
  - Definition: ↑Cr ≥0.5 or 25% within **48-72h** of contrast without other causes
  - Clinical syndrome: starts 24-48h**, peaks 3-5d**, resolves 10d; usually non-oliguric. Recent studies: unclear risk of AKI following contrast, likely lower than previously estimated (Ann Em Med 2017;69:577). In recent regression discontinuity analysis, no difference in kidney function at 6 months after contrast administration for CTPE in ED setting (JAMA Intern Med 2021;181:767)
  - Pathophysiology: vasospasm vs acute tubular injury due to osmotic injury.
  - Risk factors: higher contrast load, hyperosmolar contrast, intra-arterial injection (cardiac cath), DM, proteinuria, concomitant AKI
  - Prophylaxis: for high-risk pts (GFR <30 or 30-45 + DM) receiving arterial/IV contrast, consider IV NS per MGH protocol (see *Contrast*). If treating volume overload, hold diuretics day of contrast with no additional IVF. No added benefit for IV bicarb or NAC (NEJM 2018;378:603) or pre/post/intra HD for anuric patient (Am J Med 2012;125:66).
  - Rule of thumb: balance risk as detailed above with potential harm of delayed diagnosis that guides treatment on individual basis.
- **Crystalline nephropathy**: discontinue drug; fomepizole/HD if ethylene glycol toxicity; rasburicase/HD if TLS (*see Tumor Lysis Syndrome*); IVF and diuresis if Acyclovir toxicity (goal UOP >150 cc/h)
- **HRS**: see *Hepatorenal Syndrome*
- **Myeloma kidney (Cast Nephropathy)**:
  - Dx: TP/Cr, SPEP/UPEP/SFLC, kidney bx if dx unclear
  - Tx: IV hydration to target UOP >3L/d to minimize precipitation (volume overload can be treated with diuretics), chemotherapy to decrease production of SFLC per oncology. Unclear benefit of plasmapheresis given rebound of light chain production.
- **Post-renal**: Foley, α-antagonists; 5α-reductase inhibitor (effect not immediate); urology/IR if perc nephrostomy tube needed
- **Rhabdomyolysis**: AKI unlikely unless CK >2k-5k; aggressive IVF for UOP >250cc/h with NS. Consider isotonic sodium bicarb if marked acidosis (NEJM 2009;361:62) and no hypocalcemia, but no convincing evidence HCO3 is superior to NS. Monitor for electrolyte abnx: hyperK, hypoCa. Continue aggressive IVF until CK <5000; if overloaded, continue IVF with close monitoring and diuresis

Nephrology Glomerular Disease

NEPHROTIC SYNDROME (NS)

Etiology: ↓podocyte integrity or presence -> glomerular proteinuria (predominantly albumin)
Presentation: Constitutional sx (fatigue, anorexia), HLD + premature atherosclerosis, foamy urine, hypercoagulability (10-40% VTE risk 2/2 loss of antithrombin & plasminogen), Vit D deficiency (loss of binding protein), infectious risk (↓IgG/opsonins), protein malnutrition
Diagnosis: spot urine PCR> 3000mg/g confirmed by 24h UPr >3.5 g/d AND albumin <3.5 (distinguishes from nephrotic range proteinuria). Note that low and high muscle mass will over and underestimate proteinuria on spot ratios, respectively.
Work up: UA, Hgb a1c**,** ANA, anti-dsDNA, anti-PLA2R, THSD7A, SPEP/SFLC, HBV, HCV, HIV, syphilis, cryoglobulins, C3/C4, renal bx
Treatment: Edema: diuretics + low Na diet; HLD: statin; VTE risk: consider ppx or therapeutic AC; ACE/ARB (↓glom pressure). May consider steroids. See KDIGO 2021 guidelines.

Disease	Associations	Biopsy Findings
Diabetes	T1DM and T2DM, retinopathy/neuropathy; MCC of adult NS	Nodular glomerulosclerosis
FSGS	1°: toxin or circulating permeability factor → podocyte effacement 2°: viral (HIV, parvo, EBV, CMV), drugs (NSAIDS, pamidronate, INF, rapamycin, heroin), adaptive (2/2 nephrectomy, CKD, obesity, reflux, HTN), chronic hypoxemia (OSA, sickle cell)	Mesangial collapse & sclerosis. Collapsing variant (a/w HIV & SLE) rapidly progresses to ESRD
Membranous	1°: Abs to podocyte PLA2R (75%) (NEJM 2009;361:11) or THSD7A 2°: SLE, HBV, syphilis, drugs (NSAIDs, penicillamine, gold), solid tumors	Thick BM w/dense subepithelial deposits & no cellular infiltrates
Minimal Change	Idiopathic, a/w NSAIDs, lymphoma (HL most commonly), children>adults	Podocyte effacement (EM)
MPGN	**Immune complex mediated**: **Chronic Infxn** (HCV>HBV, endocarditis, abscess**); Autoimmune:** SLE> sjogren's, RA; **Monoclonal gammopathies; Other:** Lymphoma, solid tumor cancers. **Complement-mediated**: dense deposit disease or C3/C4-glomerulonephritis	Thick BM, mesangial proliferation, subendothelial ± subepithelial deposits
Amyloidosis	AL (myeloma) and AA (systemic inflammation, e.g. RA, IBD)	Diffuse amorphous hyaline glomerular deposits; +Congo red. IF κ/λ, LC if AL

GLOMERULONEPHRITIS (GN)

Etiology: Immune-mediated inflammation of the glomerulus leading to endothelial and podocyte injury → hematuria w/ active sediment
Presentation : AKI, HTN, edema, proteinuria, hematuria, hypercoagulability, rapidly progressive azotemia. If systemic vasculitis, often fatigue, fever, weight loss, small-vessel involvement of other organ systems (palpable purpura, DAH, mononeuritis multiplex), SLE sx

1) Asx urinary abnormalities: subnephrotic proteinuria +/- microscopic hematuria; no renal impairment, edema, or HTN
2) Rapidly progressive GN (RPGN): **↓GFR >50% in ~3 mo**, glomerular crescents on bx, 0.5-2.5 g/d proteinuria, dysmorphic RBC.
3) Chronic GN: persistent proteinuria, +/- hematuria, slow progression

Workup: UA/sed (dysmorphic RBC; specific, less sensitive), RBC casts (rare, very specific), sub-nephrotic proteinuria (<3.5g/d, but 10-30% >3g/d). Consider serololgic work up as per below. **Early renal consult for consideration of biopsy.**
Treatment: Tx of etiology (abx, antivirals, removal of offending drug), BP mgmt, diuresis, low Na diet. Sparsentan approved for tx of IgA nephropathy (Lancet 2023;401:1584). Bx will guide immunosuppression, but if severe RPGN, consider empiric IV methylpred pulse (0.5-1 g x3 days) as you await bx followed by cyclophosphamide (CYC) or rituximab (RTX). **RPGN from ANCA vasculitis**: induction w/ steroids + RTX or CYC (NEJM 2010;363:221); maintenance w/ RTX > AZA (NEJM 2014;371:1771). Induction w/o PLEX and w/ ↓-dose steroids appears non-inferior and ↓ infx risk (NEJM 2020;382:622).

Disease	Associations	Labs
Renal-Limited Immune Complex Deposition		
Post-strep GN	~1-2w post-pharyngitis, 3-6w post-cellulitis	⊕ASO, ↓C3
Fibrillary GN	Idiopathic; cancer; autoimm (Crohn's, SLE, Graves', ITP)	Normal C3 (bx IF +DNAJB9)
IgA nephropathy	1°: ~1-2d post-viral URI or GI infx. 2°: liver dx, Celiac, HIV	+/- ↑IgA, nl C3
Systemic Immune Complex Deposition		
SLE (Classes 3, 4)	Photosensitivity, malar rash, sicca, pleuritis, cytopenias, arthralgias	⊕ANA, ⊕anti-dsDNA, ⊕anti-Sm, ↓C3, ↓C4
Cryoglobulinemia (Type 2)	HCV > HBV, ESLD, MM	⊕Cryos (↑↑⊕RF), ⊕HCV, ↓C3, ↓↓C4
Endocarditis	Fever, valve dx, emboli	⊕BCx, ↓C3, ANCA (⊕can be induced)
IgA Vasculitis (HSP)	Post-URI, malignancy, nephropathy, purpura, arthritis, GIB	⊕IgA, nl C3 (IgA does not fix complement)
Pauci-Immune Glomerulonephritis		
Granulomatosis with polyangiitis	Granulomatous sinusitis/otitis, other ENT sx, pulm sx (DAH, granuloma), arthritis, palpable purpura, RPGN	c-ANCA/anti-PR3 (80%), p-ANCA/anti-MPO (10%)
Eosinophilic granulomatosis w/ polyangiitis	Multi-system, new-onset asthma, allergic rhinitis/sinusitis, mononeuritis multiplex	p-ANCA/anti-MPO (50%), eos ≥1500
Microscopic polyangiitis	Multi-system, non-granulomatous	Anti-MPO (60-70%)
Drug-induced vasculitis	Hydralazine, PTU, allopurinol, adulterated cocaine (levamisole → ear necrosis)	↑-titer p-ANCA (95% drug-ind; MPO, HNE); c-ANCA (50%; anti-histone)
GBM Diseases		
Anti-GBM/Goodpasture	RPGN (crescentic), DAH (Goodpasture)	Linear IgG along BM, ⊕anti-GBM IgG
Alport	Mutant COL4A (renal, hearing, eye dx), familial	EM w/ split GBM, ⊕COL4A3-5 testing

Nephrology

Chronic Kidney Disease

OVERVIEW

- CKD definition: GFR <60mL/min OR kidney damage (albuminuria ≥30mg/d for ≥3mo (JAMA 2015;313: 837)
- Estimating GFR: 2021 CKD-EPI (NEJM 2021;385:1737) (race omitted). Race in eGFR calc can lead to undertreatment and transplant inequity for Black pts (NEJM 2020;383:874)
- Role for Cystatin C: protein excreted by cells, less affected than Cr by gender, age, body size, nutritional status (Expert Rev Mol Diagn. 2020; 20(10): 1019). Input w/ Cr into combined 2021 CKD-EPI eGFR calculator.
- Etiology: **DM (47%), HTN (28%)**, GN (7%), cystic kidney (3%), other (15%) (USRDS 2018)
- Epidemiology: 15% US adults; ESRD prevalence 4-fold higher in Black pts than White pts (USRDS 2021). 13% of Black individuals have a high-risk **apolipoprotein-1 (ApoL1)** genotype, which confers ↑CKD risk
- Disease Monitoring: G1-G3a: risk factor reduction. G3a-G3b: evaluate & treat complications. G4 (or A3): nephrology referral, prep for RRT/transplant. G5: RRT (if indicated), transplant eval

Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999-2006. Colors represent risk for progression, morbidity, and mortality: green (low), yellow (moderate), orange (high), red (very high). Lancet 2012;379:165

GFR categories (ml/min/ 1.73m²) Description and range				Persistent albuminuria categories Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30-300 mg/g 3-30 mg/mmol	A3 Severely increased >300 mg/g >30mg/mmol	
	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	60-89	32.9	2.2	0.3	35.4
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.2	4.6
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.6
	G4	Severely decreased	15-29	0.2	0.1	0.1	0.4
	G5	Kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

MANAGEMENT

- BP control: goal <120/80 (KDIGO 2024 guidelines). Mortality benefit w/ intensive BP mgmt (SBP <120 mmHg) (NEJM 2021;384(20)).
  - *If proteinuria*: ACEi; *if edema*: loop diuretic if eGFR <30, thiazide if >30 (emerging evidence for considering chlorthalidone in advanced CKD in select pts) (NEJM 2021;385:2507); *if resistant HTN or HFrEF/HFpEF*: spironolactone.
- Proteinuria: Albuminuria independently predicts mortality and CKD progression w/ tx goal as <300mg/d. Start w/ RAAS blockade (**ACEi or ARB**) uptitrated as tolerated (NEJM 2013;369:1892). If albuminuria >300 mg/d or proteinuria >500 mg/d, **add SGLT2-i** if eGFR>20-30 to ↓ CKD progression (NEJM 2022;388:117). If CKD a/w diabetic kidney disease w/ GFR ≥ 25, ACEI/ARB maximized + SGLT2i started + K ≤ 4.8 + continued albuminuria ≥ 30mg/d, consider **finerenone** (non-steroidal MRA shown to reduce CV risk primarily by reduction in HF exacerbations). Watch out for cost and ↑K+ when starting finerenone (KDIGO 2024 guidelines).
- DM: goal HgbA1c <7%. SGLT2i (if eGFR >20-30) indicated in pts with T2DM and DKD (BMJ 2021;372:4573), other agents include metformin (eGFR >30-45), GLP-1r agonists (eGFR >30). Insulin safe at any eGFR, though may have to be dose adjusted as insulin clearance ↓ w/ ↓GFR. ↓Rate of CKD progression with SGLT2i (NEJM 2019;380:2295) & GLP-1r agonists (NEJM 2017;377:839).
- CVD: risk 2-4x general population. Statin if >50 y/o and no ESRD/tx (Kidney Int 2014;85:1303). SGLT2 inhibitors ↓CKD progression/mortality/CVD outcomes. (NEJM 2020;383:1436). No benefit seen in initial invasive vs. conservative strategy in stable CAD + advanced CKD, and mod/sev ischemia (NEJM 2020;382:1608)
- Nephrotoxins: **Avoid** NSAIDs, chronic PPI's, contrast, select and dose meds renally (abx, tacrolimus, statins, opiate pain meds)
- Nutrition: nephrocaps (B-complex / C), Na <2 g/d, ↑ fruit/vegetable intake, ↓protein to 0.8 g/kg for non-nephrotic CKD w/ eGFR <60, restrict K/Phos prn
- Monitoring: q4-12mo Cr & electrolytes, PTH, CBC, Fe studies. Annual UAlb/Cr & UProt/Cr ratios, 25-OH Vit-D. Renal U/S at dx
- Nephrology referral: GFR ↓ 30, sudden ↓ in GFR, severe proteinuria (Alb:Cr >300), UA w/ +blood/protein with ↓GFR, resistant HTN
- Prognosis: based on 1) cause of CKD, 2) GFR category, 3) albuminuria, 4) other risks→ Tangri risk score (JAMA 2016;315:164)

COMPLICATIONS

Hyperparathyroidism					
Type	**Ca**	**PO_4**	**PTH**	**VitD**	**Pathophysiology**
1° HyperPTH	↑	↓	↑	nl	Excess PTH production by parathyroid gland
2° HyperPTH (2/2 ↓VitD)	↓	↓	↑	↓	Decreased Ca absorption stimulates PTH secretion
2° HyperPTH (2/2 CKD)	nl/↓	↑	↑	nl/ ↓	↓ PO4 excretion increases PTH secretion
3° HyperPTH	↑	↑	↑↑	nl/ ↓	Longstanding 2° hyperPTH leads to PTH gland hyperplasia

- Mineral and bone disorder: check Ca, PO_4, ALP, 25-OH vit D (1,25-OH vit D level will fluctuate) (Annals 2018;168:422).
  - PTH rising or persistently above goal (2-9x ULN, based on CKD stage): restrict dietary phos, non-Ca phos binders (sevelamer preferred, w/ meals & snacks) (CJASN 2016;11:232), calcium/Vit D supplements not recommended unless on HD
  - Severe/refractory PTH > 1000: calcitriol vs calcimimetic vs parathyroidectomy if non-responsive to medical therapy
- Anemia: Hgb < 13 (M), < 12 (F). **Screening**: annual if eGFR >45, q6m if <45, q3-6m if anemic. Goal Hb 10-11.5 (Kidney Int 2012)
  - Iron repletion (PO or IV): Consider 1 gram IV iron empirically if Tsat <20% and/or ferritin <100ng/mL. If TSAT is 20-30% and ferritin <500, can consider challenging with iron or starting an ESA. Check q3m if on ESA. (Cochrane 2019;2:7857)
  - If Fe replete and Hgb <10, consider erythropoiesis stimulating agents (ESA) consider ESA, which ↓ transfusions, Fe overload, Ab formation. Contraindicated in cancer, SBP>160, HF, stroke. Hb >13 with ESA increases risk of CVA (NEJM 2009;361:2019)
- Metabolic acidosis: $NaHCO_3$ starting at 650 mg 2-3x/day titrating up to 1300 mg up to TID for goal HCO_3 in normal range (23-29 mEq/L; avoid >29 mEq/L bc ↑ mortality). Slows progression of CKD, improves bone health (CJASN 2019;14:1011)
- Uremic bleeding: Treat depending on clinical context or if pre-procedure; can use DDAVP 0.3-0.4 mcg/kg x1 with max 40 mcg
- Preparation for HD access: avoid BP measurements and venipuncture in non-dominant arm, avoid subclavian/PICC lines due to risk of central stenosis (precludes future AVF placement) → prefer IR small bore tunneled IJ. Prefer LIJ CVC in case need for HD

Nephrology

Dialysis & Transplant

OVERVIEW (NEJM 2022;386(10):964)

Diffusion: concentration gradient drives small molecules (e.g. urea, creatinine) across selectively permeable membrane
Convection: hydrostatic pressure forces medium-weight molecules across membrane
Ultrafiltration (UF): volume removal, removal of plasma water by hydrostatic pressure

Emergent Indications for RRT (AEIOU)
Acidosis: metabolic, pH <7.1
Electrolytes: refractory/rapidly rising K
Ingestions: dialyzable toxins (eg: Li, ASA, methanol, ethylene glycol, metformin)
Overload: diuretic-refractory volume
Uremia: encephalopathy, pericarditis, coagulopathy with uremic bleeding

IMPORTANT CONSIDERATIONS

Timing: controversial, most recent studies suggest no benefit to early RRT

- ELAIN (JAMA 2016;315:2190): early RRT→↓duration RRT, LOS/mortality
- IDEAL-ICU (NEJM 2018;379:1431): no ∆mortality w/ early RRT (pt w/ sepsis, AKI)
- STARRT-AKI (NEJM 2020;383:240): early RRT did not reduce 90d mortality vs. standard RRT (clinical indication).
- AKIKI-2 (LANCET 2021;397:1293): delayed RRT in oliguria >72h or BUN >112 until clinical indication showed ↑mortality

ACCESS FOR HEMODIALYSIS

- Dialysis lines can only be accessed by dialysis/ICU RNs (except in codes); contact dialysis unit (x63700).
- PICCs: HD or future HD candidates should not receive PICC unless first cleared by Renal (to preserve options for vascular access)

Types of access for HD	Durability	Benefits	Risks/Downsides
Non-tunneled double lumen central line, femoral or R IJ	Days-weeks	Can be placed and used immediately.	Infection. Can clot or kink. ONLY to be used for RRT while admitted.
Tunneled central line	Weeks-mos, can be yrs	Can be placed by IR within hrs. Can be used as an outpt.	Infection and clot. ONLY to be used for RRT. Long term risk of central venous stenosis
AV fistula (pt A-V)	Yrs	Lowest infection and clot risk. Associated with increased survival	~3-6 mos to mature, 1° failure in ~40%. Limb edema, aneurysm/stenosis/clot, vascular steal, high output CHF
AV graft (synthetic graft connects A-V)	Yrs	Useable in days-wks. Lower infection and clot risk than central access.	Delayed failure (~25%) 2/2 stenosis/thrombosis. Risk of aneurysm. Infection requires surgical resection.

INTERMITTENT HEMODIALYSIS (IHD) (NEJM 2010;363:1833); consider in critically ill pts (Lancet 2006;368:379)

- Mechanism: Cr, urea, K^+ move from blood to dialysate; Ca^{2+} and HCO_3^- move from dialysate to blood (diffuse via concentration gradients). Volume removal occurs via UF. Blood flow rate ~200-500mL/min. Usually three 4h sessions/wk.
- Intradialytic medications: erythropoietin, iron, vitamin D analogues, antibiotics, heparin (to prevent clotting of HD circuit)
- Complications: HoTN, arrhythmia/cardiac events, cramps, disequilibrium syndrome, dialyzer reaction, HIT, hemolysis, EtOH w/d

PERITONEAL DIALYSIS (PD) (NEJM 2021;385:1786)

Daytime: PD RN (617-726-0717)

- Mechanism: infusion of fluid rich in osmotic agent (e.g. dextrose) → use peritoneum as membrane→ solute removal via diffusion
- Benefits: preserves residual GFR longer than IHD, better middle molecule clearance, can be done at home.
- Modalities: (1) continuous ambulatory PD (**CAPD**) manual exchanges occurring day and night (2) nocturnal intermittent peritoneal dialysis (**NIPD**) w/ dwells only at night (3) automated PD (**APD**) multiple automated exchanges overnight w/ long daytime dwell
- Complications: Encapsulating peritoneal sclerosis, hernia, pleural effusion, leaking, hypoK (dialysate has no K). **Peritonitis** (dx 2/3: 1) abd pain/cloudy fluid 2) effluent fluid WBC >100 w/ >50%PMNs (after >1-2 hr dwell) 3) +effluent fluid culture (see ellucid). Treat after culturing w/ IP vanc/ceftazidime (use IV gram+&- coverage if septic). Remove catheter if no resolution w/in 5d or if fungal infxn.

CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

- Principles: continuous slow clearance, replacement fluid must be added back to restore volume, A/B balance + electrolytes. Less effective in toxin removal/volume overload compared w/ IHD. Not ideal for hyperK/toxins. Blood flow rate ~100-200mL/min.
  - **CVVH**: continuous veno-venous HF, removes solute via convection; **AVVH**: intermediate CVVH circuit setting w ↑flow rates/12h
  - **CVVHD**: continuous veno-venous HD, removes solute by diffusion; **CVVHDF**: combines convection + diffusion to remove solute
- Indications: (1) **HD instability**/inability to tolerate iHD (2) persistent acidemia despite iHD (3) risk of cerebral edema w/ iHD.
- Volume management: run negative, even, or slightly positive. Replacement fluid w/ dextrose, bicarb, lactate, acetate or citrate.
- Anticoagulation: used to ↓risk of circuit clotting, use heparin OR citrate, citrate achieves regional AC by Ca chelation → follow iCa levels (will↑total Ca but ↓iCa), metabolized in liver → if Ca_t/iCa >2.5,↑AG with met alk=possible citrate toxicity (avoid in liver failure).
- Complications: HoTN, arrhythmias, hypothermia,↓iCa/K/PO4, bleeding, thrombocytopenia (mechanical destruction), HIT
- Drug dosing: drugs can bind to circuit resulting in ↑V_D → work with pharmacy to re-dose all meds based on flow rate

RENAL TRANSPLANT

- Basics: mortality & QOL benefit, more cost-effective than HD; LDKT > DDKT; racial disparities exist in transplant access
- Listing: refer EARLY (GFR <30), pts can be listed when GFR <20; pt & graft survival are improved if transplant occurs PRIOR to HD
- Contraindications: short life expectancy, active malignancy, SUD, nonadherence. *Age/HIV/psych comorbidities NOT contraindications*
- Allograft dysfunction: **delayed graft function**: <1w (prerenal, ATN, thrombus, obstruction), **early**: 1-12w (prerenal, CNI tox, infxn [BK virus, CMV], acute rejection), **late acute**: >3mo (prerenal, CNI tox, noncompliance), **late chronic**: yrs (HTN, CNI tox, BK virus, recurrence of original renal pathology, chronic allograft nephropathy)

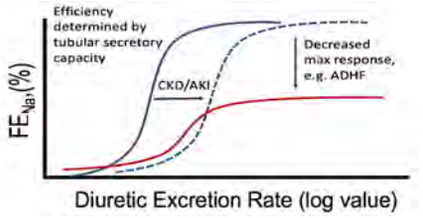
IMMUNOSUPPRESSION			
Class	**Examples**	**Mechanism of Action**	**Adverse Events**
Calcineurin inhibitor (CNI)	Cyclosporine Tacrolimus (FK506)	Inhibits calcineurin-mediated activation of NFAT → blocks T-cell cytokine production	Nephrotoxicity (long-term fibrosis), HTN, tremor, insomnia, hirsutism (CsA only)
mTOR inhibitor	Sirolimus (Rapamycin)	Inhibits mTOR → blocks IL-2 production	Pulm edema, poor healing, ↑TG, oral ulcer
Antimetabolite	Mycophenolate	Inhibits de-novo purine synthesis	N/V/D, cytopenias
	Azathioprine	Purine analogue	BM suppression, N/V/D, hepatitis

Nephrology

Advanced Diuresis

General Principles

- Obtain daily standing weights, Na^+ restriction 2g/day + fluid restriction 1.5-2L
- Loop diuretics have a sigmoidal dose-response curve (i.e. diuretic threshold effect), so double dose until adequate response is achieved
- Transient ↑ in serum Cr are common in diuresis (~20% of cases in DOSE-AHF, ROSE-AHF), can be tolerated if effective decongestion. No assoc. between ↓renal function during diuresis and biomarkers of tubular injury; rather, associated with better outcomes in HF (Circ 2018;137:2016, JCF 2016;22:753).



	Loop Diuretics (Loop of Henle)			Thiazide Diuretics (DCT)
	Furosemide	**Torsemide**	**Bumetanide**	**Chlorthalidone, HCTZ (PO) Metolazone, Chlorothiazide (PO/IV)**
Mechanism of Action	Inhibit Na-K-2Cl transporter in asc. limb of loop of Henle to ↓Na reabsorption and "break" medullary concentrating gradient			Inhibit NaCl channel in DCT to ↓Na reabsorption and prevent urinary dilution
PO Bioavail.	20-50%	80-90%	80%	Variable
Duration of action	~6 hours	6-8 hours	4-6 hours	HCTZ: 6-12h; chlorthalidone: 24-48h metolazone: 24h; chlorothiazide (IV): 2h
Dosing considerations	1mg Bumetanide IV/PO = 20mg Torsemide PO = 20mg Furosemide IV = 40mg Furosemide PO. Consider dosing BID-QID to avoid anti-natriuresis seen in QD dosing (see NEJM 2017;377:1964 Fig. 2C)			Administer metolazone 2.5-10mg PO or chlorothiazide 500-1000mg IV 30 min before loop diuretic to "disable" Na reabsorption in DCT (**sequential nephron blockade (SNB)).**
Side effects	**↑Na, ↓K, ↓Mg**, ↓Ca, ↑urate, ↑HCO_3, ototox, allergy			**↓Na** (avoid if SIADH)**, ↓K, ↓Mg**, ↑Ca, ↑urate, ↑glucose, HLD, pancreatitis, MBD

Disease-Specific Considerations

Condition	Mechanism	Treatment
CKD/AKI	• ↓GFR → ↓delivery of diuretic to nephron → **higher** doses needed for effective diuresis • Organic acids accumulate and compete with diuretics	• High-dose loop ± thiazide augmentation *(prefer Furosemide in CKD given renal excretion, longer ½ life)*
Chronic Diuretic Use	• "Braking phenomenon" of compensatory DCT hypertrophy leads to ↑ distal Na reabsorption	• Add metolazone or chlorothiazide
CHF	• In ADHF, GI edema leads to ↓absorption of PO diuretics • High sympathetic tone → ↑RAAS, Na reabsorption	• DOSE (NEJM 2011;364:797): in ADHF, no Δ sx or renal fx for pts receiving drip vs bolus dosing • Consider **SNB** (see Stepwise Approach in CHF)
↓ Albumin, nephrotic syndrome	• Loop diuretic (needs to bind to albumin) leaks out of vasculature (↑V_D) resulting in ↓delivery to nephron	• Consider bumetanide (lower albumin-binding need) • No evidence for benefit of albumin + loop diuretic
Cirrhosis	• Decreased delivery to nephron in setting of ↓ albumin • Splanchnic vasodilation → ↓EABV → renal hypoperfusion • SNS and RAAS → ↑Na reabsorption	• **Avoid IV diuretics** unless respiratory distress or significant peripheral edema • See *ESLD: Ascites*

Other Diuretics and Stepwise Approach in Heart Failure (NEJM 2017;377:1964)

1. IV loop diuretic. Starting dose: 2x-2.5x home dose as IV furosemide (CHF) (e.g. if home 80mg PO lasix, give ~80-100mg IV) or Cr×40 as IV furosemide (e.g. if Cr 3, use lasix 120mg IV)
2. Reassess in 1-2 hrs and double dose Q1-2H until response achieved. Adequate dose causes brisk diuresis (Goal >100-150 cc/hr).
    a. Consider loop diuretic gtt (bolus when initiating gtt and re-bolus every time gtt increased), though evidence suggests not more effective in ADHF (NEJM 2011;364:797).
3. If refractory edema, consider augmentation to achieve SNB. Selection of agents should be tailored to severity of overload, clinical setting, long term benefits, labs, and ability to replete Mg/K.
    a. **Chlorothiazide**: short term augmentation or diuretic challenge is required inpatient, can help with hypernatremia
    b. **Metolazone:** when a longer duration of augmentation is required inpatient or outpatient, can help with hypernatremia
    c. **Acetazolamide**: **PCT blockade**. Acetazolamide IV 500 mg daily in addition to a loop diuretic, especially if metabolic alkalosis limiting diuresis. (↑HCO3, pH >7.45). ADVOR (NEJM 2022;387:1185) showed better decongestion when added to loop diuretics in ADHF compared to loop diuretics alone when used daily for 3 days. Caution in COPD, acidosis, and sulfa allergies.
    d. **Aldosterone Antagonists**: Spironolactone: 12.5-200 mg / eplerenone 25-50 mg QD. Role in CHF/Cirrhosis. Causes ↑K, gynecomastia (10% pts, only spironolactone). Useful when hypokalemia is limiting diuresis and minor augmentation needed.
    e. **SGLT2i:** Modest diuretic effect started closer to DC (Circ 2022;146:289). Maintenance diuretic may need to be variably decreased when starting. Caution in pts w/ frequent UTIs, AUD, and ↓ PO intake.
4. Nephrology consult for consideration of short term UF/RRT as a bridge to renal recovery or advanced therapies
5. If starting maintenance loop diuretic at discharge, no strong evidence to prefer torsemide over PO furosemide (TRANSFORM-HF: JAMA 2023;329:214), but make sure to adjust the amount of maintenance diuretic if also discharging w/ MRA or SGLT2i.
6. Be conscious of potassium repletion during hospitalizations and discharge with standing K repletion or increased MRA if needed.

Nephrology

Acid-Base Disorders

OVERVIEW

- **ABG vs VBG**: VBG pH ~0.04 lower, HCO_3 ~2mEq lower (BMP more accurate), CO_2 ~3-8 mmHg higher. VBG can screen for hypercapnia w/ pCO2 cutoff ≥45mmHg (100% Sn) but does **NOT** accurately assess degree of hypercapnia. VBG PCO_2 non-correlative in severe shock. **When in doubt, check ABG** (AJEM 2012;30:896).
- Severe acidemia (pH <7.2) may precipitate systemic vasodilation, ↓inotropy/MAP, ↓response catechols/pressors, arrhythmia, ↑K, insulin resist., AMS
- Severe alkalemia (pH >7.6) may precipitate systemic vasoconstriction, ↓coronary/cerebral perfusion, SVT/VT, ↓K/Ca/Mg/Phos, AMS, seizure, hypoventilation

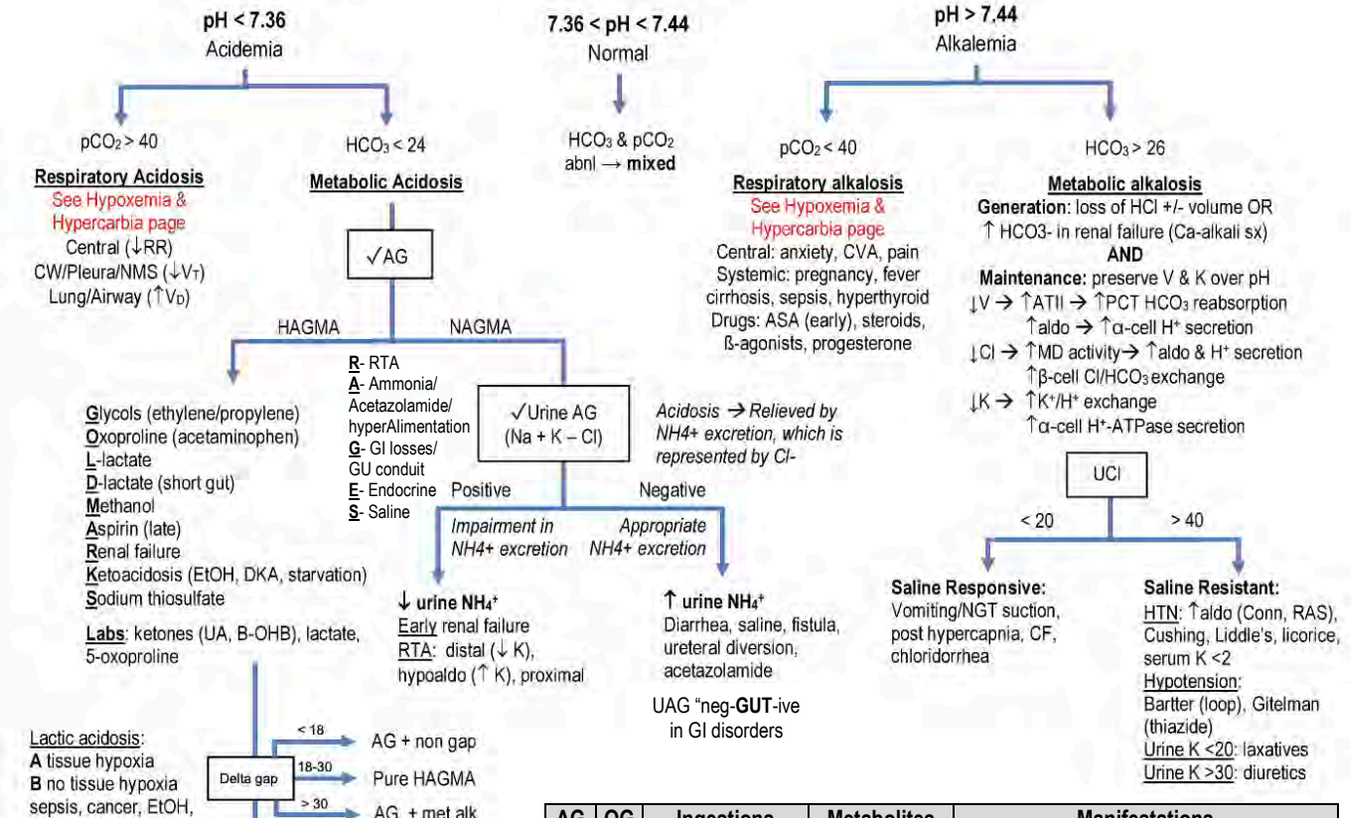
STEP-WISE APPROACH (NEJM 1998;338:26; NEJM 2014;371:1434)

1. Is there acidemia (pH <7.36) or alkalemia (pH >7.44)?
2. Is 1° disorder metabolic (parallels pH Δ) or resp (opposite pH Δ)?
3. Is pt compensating? (respiratory takes min-hrs, renal 3-5d)
4. Is there an anion gap? Calculate regardless of pH or HCO_3
   AG = Na – (Cl + HCO_3) = unmeasured anions – unmeasured cations
   Correct AG for albumin: AG_c = AG + 2.5(4 – albumin)
   Negative AG: ↑↑Na or other cations (Ca, Mg, Li), lipids (interfere with chloride), protein (multiple myeloma), bromide or iodine intox,
5. If there is ↑AG metabolic acidosis (AGMA), calculate "**delta-gap**"
   Delta gap = (Albumin corrected AG-12) + HCO_3. If <18 additional NAGMA**, 18-30** no additional disorder**, >30** additional met alk
6. Consider Osm gap = [2(Na + K) + Urea/2.8 + glucose/18 + EtOH/4.6 – serum Osm] to screen for exogenous osmoles (e.g. toxic alcohols), also seen in pseudohyponatremia

Expected Compensation (JASN 2010;21:920)

Metabolic acidosis: 2-24h
Winter's formula: $pCO_2 = (1.5 \times HCO_3) + 8 \pm 2$
Metabolic alkalosis: start 30min, complete 24h
$PaCO_2 = 0.7 \times (HCO_3 - 24) + 40 \pm 2 = HCO_3 + 15$
Δ HCO_3 ↑ 1 → expect Δ pCO_2 ↑ 0.7
Respiratory acidosis:
Acute: Δ pCO_2 ↑ 10 → Δ HCO_3 ↑ 1 or ↓ pH 0.08
Chronic: Δ pCO_2 ↑ 10 → Δ HCO_3 ↑ 4 or ↓ pH 0.03
Respiratory alkalosis:
Acute: Δ pCO_2 ↓10 → Δ HCO_3 ↓ 2 or ↑pH 0.08
Chronic: Δ pCO_2 ↓10 → Δ HCO_3 ↓ 4 or ↑pH 0.03

ALGORITHMIC APPROACH



AG	OG	Ingestions	Metabolites	Manifestations
↑	↑	Methanol	Formic acid	ΔMS, blurry vision, pupil dilation, papilledema
		Ethylene glycol	Oxalic acid	ΔMS, CN palsy, GU symptoms (flank pain, hematuria), tetany 2/2↓Ca, Ca oxalate crystals → AKI
		Propylene glycol	Lactic acid	AKI, liver injury
		Diethylene glycol	Diglycolic acid	AKI, n/v, hepatitis, pancreatitis, neuropathy, later ΔMS,↑ lactate
nl/↑	↑	Isopropyl alcohol	Acetone	ΔMS, fruity breath, pancreatitis, ↑ lactate
		Ethanol	Acetaldehyde	Keto/lactic acidosis ± met. alk 2/2 emesis

MANAGEMENT OF ACID-BASE DISORDERS: treat the underlying cause!

- **Metabolic acidosis**:
  - Acute:
    - In BICAR-ICU (Lancet 2018;392:31), pts with metabolic acidosis (pH <7.2) tx w/ IV HCO3 for goal pH >7.3 had no Δ in overall mortality but ↓RRT initiation. A subset of pts w/ AKIN stages 2-3 had improved mortality at 28d
    - For pH <7.1 or HCO_3^- <6: if HDS, can start **isotonic HCO3 gtt**. Monitor VBG/ABG q1h + electrolytes (K, iCa) and volume status. Bolus admin is controversial due to c/f CO2 accumulation → hypercapnia (acidosis), hypernatremia, hypocalcemia, hypertonicity, hypervolemia, overshoot alkalosis
    - For bicarb to have full effect on serum pH, pt must be able to increase minute ventilation to ventilate off CO_2
  - Special considerations:
    - Toxic alcohols: call poison control, NaHCO3, **fomepizole**, or HD (if vision Δ, AKI, HAGMA, methanol >50mg/dL, ethylene glycol >300mg/dL)
    - Salicylate poisoning: NaHCO3 to goal urine pH >6.5 and serum salicylate level <40 or HD (if level >80mg/dL, coma, AKI, hypervolemia, AMS), dextrose containing fluids if AMS. **Acetazolamide is contraindicated**
    - NAGMA and uremic acidosis are more responsive to HCO3 than lactic and ketoacidosis
  - Chronic: in CKD, replete with PO NaHCO3 for goal HCO_3 >22. See *CKD*
- **Metabolic alkalosis**: replete volume, K, & Cl
  - Treat both (1) underlying cause of metabolic alkalosis and (2) cause of renal retention of HCO_3
  - If saline responsive: **NS w/ KCl** until urine pH >7. For pts w/ CHF/cirrhosis & alkalosis 2/2 diuresis, consider Acetazolamide and/or K+ sparing diuretic. See *Advanced Diuresis*
  - If saline resistant: for mineralocorticoid excess → use K^+-sparing diuretic (**prefer amiloride, faster than spironolactone**) & consider surgical removal of adenoma
  - If pH >7.6 & persistently volume overloaded, give **acetazolamide** + loop diuretic with close K^+ monitoring. May need KCl
- **Respiratory acidosis**: treat underlying process; adjust vent settings if intubated. $NaHCO_3$ unlikely to be helpful, theoretically harmful if unable to ventilate subsequent CO_2 produced. For every 100mEq HCO_3 administered, 2.2L CO_2 must be exhaled.
- **Respiratory alkalosis**: address underlying cause (correct hypoxemia, treat pain/anxiety/fever); adjust vent settings if intubated

RENAL TUBULAR ACIDOSIS (RTA) (Int J Clin Pract 2011;65:350)

Consider in select pts w/ Hyperchloremic NAGMA or hyperK (Type IV). **R/o GI losses & ↑IV NS use before ordering UAG!**

Pathophysiology: inappropriate net retention of acid or inadequate reabsorption of bicarb
- In acidemia, kidney should ↑NH4+Cl- excretion and urine pH should be <5.3; this process is defective in RTAs.
- Caveat: CKD of any etiology is associated with ↓NH_4^+ production & acidosis

Etiologies:
- Proximal RTA (Type II): decreased threshold for proximal tubule HCO_3^- reabsorption → more HCO3 spills into urine
  - Primary (rare): Na-HCO3 cotransporter defect
  - Acquired: **amyloidosis, MM**, post-renal transplant, bladder outlet obstruction, heavy metals, ↓Vit D, Wilson's disease, PNH
  - Meds: acetazolamide, cisplatin, tenofovir, aminoglycosides, topiramate
  - Often a/w Fanconi Syndrome: glucosuria (w/ serum gluc <180), hypouricemia, aminoaciduria
- Distal RTA (Type I): inability to secrete H+ in distal tubule. Various subtypes of distal RTA related to affected transporter/tight junction
  - Primary: genetic loss of H^+ or HCO3 transporters in intercalated cells
  - Acquired: **autoimmune disease** (RA, SLE, SS); **hypercalciuria** (any cause); obstructive nephropathy; SCD, MM, amyloid, cryoglobulinemia, tubulointerstitial injury, renal transplant rejection, cirrhosis, glue sniffing (toluene)
  - Meds: amphotericin B, Li^+, ifosfamide, ibuprofen, codeine
- Type IV: effective hypoaldosteronism: ↓aldo secretion OR tubular resistance → ↑K → ↓NH_3 synthesis → ↓$NH4^+$ excretion
  - Hyperkalemia inhibits glutaminase enzyme, which generates NH3 ("ammoniagenesis"). Acidosis ensues as unable to fix and excrete H+ as ammonium.
  - Hyporeninemic hypoaldosteronism (most common): diabetic nephropathy, CIN, NSAIDs, calcineurin inhibitor, HIV
  - ↓ Aldo production: ACEi/ARB > **heparin** > adrenal insufficiency, severe illness
  - Aldosterone resistance: (ENaC inhibition) K-sparing diuretic, trimethoprim, pentamidine

Workup: clinical history (PMH – autoimmune or malignancy, med review, stones), response to HCO3 supplementation
- VBG, BMP (AG, HCO_3, K), UA (pH), urine lytes. Consider urine Ca/Cr to differentiate proximal vs distal RTA
- Estimate of Urine NH_4^+: UAG = Na + K - Cl (less useful when ↑urine pH >6.5 or UNa < 25, high aldo state)

	PROXIMAL RTA (TYPE II)	DISTAL RTA (TYPE I)	TYPE IV RTA
Defect	**↓Proximal HCO_3^- resorption**	**↓Distal H^+ secretion**	**↓Distal K and acid secretion**
Serum HCO_3^-	12 – 20	<10	>17
Serum K	↓ or normal	↓ or normal	↑
Urine pH during acidemia	Varies, but >5.5 after HCO_3^-	>5.5	<5.5, but cannot buffer w/ $NH4^+$
Urine AG = Na + K – CL	⊖	⊕	⊕
Additional dx testing	Urine Ca/Cr nml, give bicarbonate and check urine pH	Urine Ca/Cr elevated	Renin, aldosterone, cortisol
Complications	Rickets, osteomalacia	CaPO4 urinary stones	Hyperkalemia
Tx (Goal HCO3 22-24)	**Challenging**. NaHCO3 (10-20 mEq/kg) or KCitrate.	NaHCO3 (1-4mEq/kg)	Treat hyperK: loop, low K diet If hypoaldo, can give fludrocort

Nephrology

Sodium Disorders

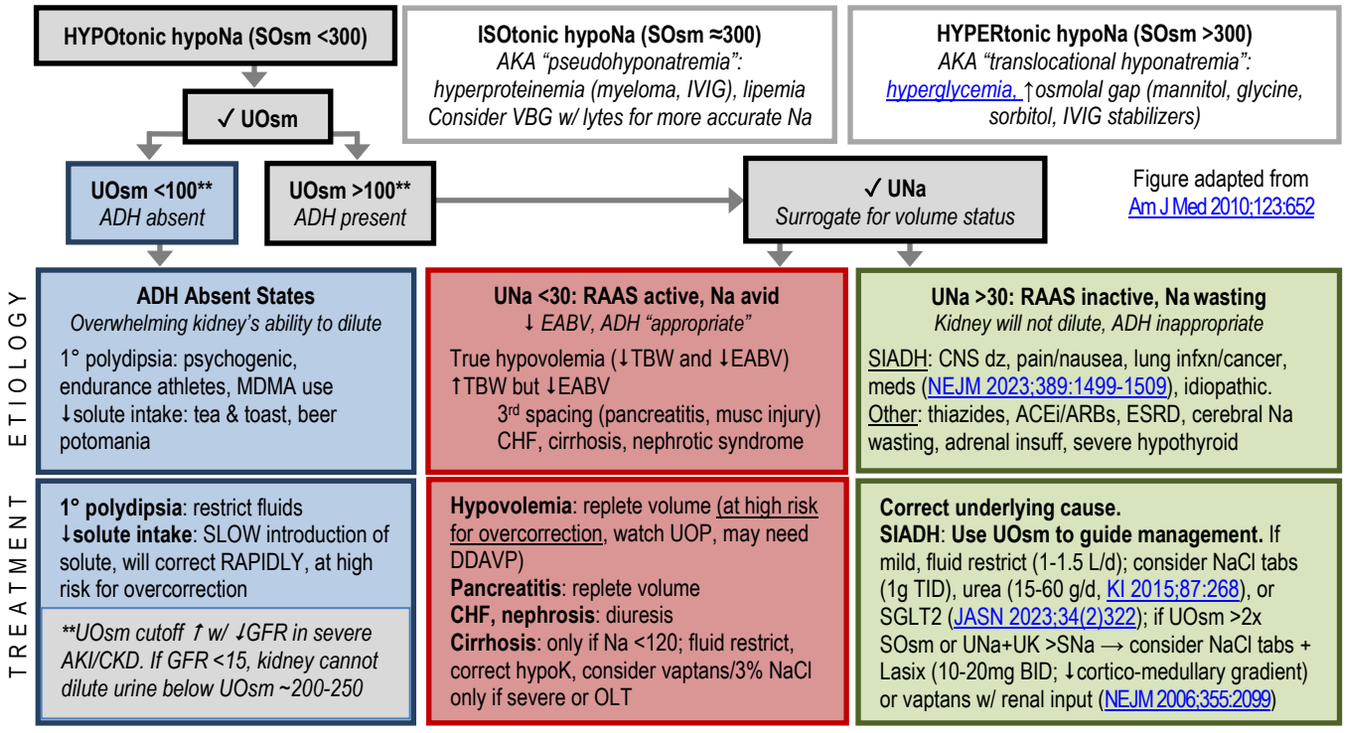
HYPONATREMIA: free water excess relative to serum sodium (JAMA 2022:328(3):280-291)

S/Sx: often asymptomatic; can present with AMS, HA, N/V, weakness, seizures, signs of increased ICP

Workup: H&P: symptoms, etiology, chronicity, new meds, endocrine ROS, volume status, surg w/ irrigation (prostate/bladder/uterine)

- Studies: *Obtain prior to treatment* Serum: BMP, Osm. Consider uric acid, TSH, AM cortisol. Urine: **UA, Osm, Na, uric acid.**
- Determine if ADH is present (**UOsm** >100**). Can approx UOsm from UA: last 2 digits of SG x 30 (e.g., SG 1.010 ≈ UOsm 300)
- Other diagnostic clues (Eur J Inter Med 2016;29:22; JCEM 2008;93:2991; Ann Intern Med 1980;93:716; Cureus 2020;12:e7762):
  - Other solutes: SIADH: often serum uric acid (sUA) <4, BUN <5, fractional excretion of uric acid (FEUA) ≥10-12% (small studies: 100% PPV for SIADH/thiazide hypoNa; FEUA ≤8% = 100% NPV for SIADH). ↓EABV: often sUA >5, BUN↑, FEUA <4%
  - IVF: SIADH: NS initially ↑SNa but then will ↓SNa (Na is excreted while H_2O retained). Hypovolemia: NS will ↑SNa

Note: Serum osm may be misleading and not reflective of serum tonicity if ineffective osms are present (BUN or ethanol)



Treatment: depends on acuity, severity, and etiology (JASN 2017;28:1340). **Renal c/s if patient needs 3% NaCl and/or DDAVP clamp**

- **Rate/goal**: ↑Na 4-6 mEq/L per 24h, to short-term goal ≥125; typically ↑Na 4-6 will alleviate sx
- **Severe symptomatic** (sz, AMS): 3% NaCl via 100mL bolus over 10 min; up to 3x until sx resolve or Na ↑5 (max 8-10 / 24h)
- **Severe asymptomatic** (Na <120): 3% NaCl at Na Correction Rate, usually 15-30mL/h, until Na ≥125; Na <120 a/w 6-10% in-hosp mortality (Clin J Am Soc Nephrol 2018;13:641). Consider proactive DDAVP clamp in high ODS risk (see **Risk Factors** below)
- **Mild/mod** (Na 130-134/Na 120-129): etiology-specific treatment (e.g., fluid repletion, fluid restriction, diuresis, hold diuresis)

Overcorrection: Na ↑ >8 in 24h or >18 in 48h. *In high ODS risk patients, some guidelines say* ΔNa *>4-6meq/24h is overcorrection*

- Osmotic demyelination syndrome (ODS): delayed onset (2-6d) dysarthria/dysphagia, paresis, behaviorΔ/AMS, locked-in synd.
  - Dx with MRI ~4w after sx onset
  - **Risk Factors**: starting Na ≤110 (ODS unlikely if starting Na >120, Hosp Pract 1995;37:128), malnutrition, EtOH use, cirrhosis, ↓K
- Be aware that rapid correction more likely in hypovolemic hyponatremia and low solute hyponatremia (CJASN 2018;13:984). Monitor for water diuresis post fluids (presents with rapid increase in UOP (>100ml/h)) and consider DDAVP clamp.
- If Na trajectory *predicts* overcorrection, consider DDAVP clamp (AM J Kidney Dis 2022;79(6):890)
  - DDAVP 2-4mcg IV/SC q6-8h with Na measured q4-6h, until Na ≥125. If needed, *add* 3% NaCl at Na Correction Rate
- If *already* overcorrected, urgently ↓Na to within previous goal (i.e., ΔNa < 8 mEq/L/24h or <4-6 mEq/L/24h in high ODS risk):
  - D5W 6mL/kg IBW over 2h (↓Na by 2) and continue with q2h Na measurements until at goal level, PLUS
  - DDAVP 2-4mcg IV/SC q6h for 24-48h even after relowering goal initially achieved

- Concurrent hypokalemia: K and Na freely exchanged, giving 1mEq of K = giving 1mEq of Na; can overcorrect w/ K supplementation

HYPERNATREMIA: free water loss in excess of NaCl loss (Crit Care 2013;17:206, NEJM 2015;372:55)

Etiologies: ↓access to free water or ↓thirst, DI

- Renal losses: UOsm <800; ↓ADH release or kidney response: post-ATN, osmotic, DI, loop diuretic, hyperCa, elderly
- Extrarenal losses: UOsm >800; GI loss from NGT, vomiting, diarrhea, insensible losses, hypodipsia

Treatment: BMP q12-24h, strict I/O. Aim to ↓SNa by 12 mEq/L per 24h (accidental overcorrection unlikely to be dangerous, complications of more rapid correction (e.g. cerebral edema) are rare in adults, CJASN 2019;14:656)

1. Calculate current free water deficit. Shortcut FWD (L) = (Current Na – Goal Na)/3. Target Na should be 24h goal
2. Account for ongoing losses:
   - Insensible losses: 700-900 mL/d typically but ↑ if burns, fever, diarrhea (cannot measure, so ↑ replenishment if inadequate)
   - Urine: 24h UOP x (1- (UNa+UK)/SNa)); alternative = (0 x 1st L) + (0.5 x 2nd & 3rd L) + (1 x urine beyond 3L)
3. FW to give today = current FWD + ongoing losses. Give via PO, TF (FWB), or IV (D5W). If DI see *Pituitary Disorders* for DDAVP

Nephrology

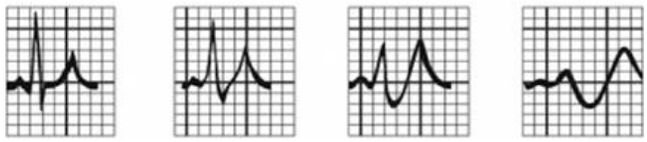
Potassium Disorders

Normal Potassium Handling/Homeostasis (NEJM 2015;373:60)

- Ingested K^+ absorbed in intestines → taken up and sequestered by liver/muscle cells via insulin & β2 receptors → ↑Na-K ATPase
- 98% of K^+ is intracellular; remaining extracellular levels trigger aldosterone secretion → principal cell K^+ secretion→ excretion in urine
- Excretion also driven by Na^+ delivery to distal nephron (macula densa). ↑Na+ delivery → K+ excretion; ↓Na+ delivery → K+ retention

Hyperkalemia

- S/S: Muscle cramps, weakness (ascending), paralysis, conduction delay (e.g. CHB, BBB, sinus arrest), arrhythmia (VT/VF, asystole, idioventricular rhythms) (CCM 2008;36:3246)
- Dx: confirm K^+ not d/t hemolyzed sample, plt>500K, WBC>120, or infusion of K^+-containing IVF; consider blood gas K^+
- ECG: peaked T waves → ↓QT→ ↑PR interval ± AVB, flat p → wide QRS ± BBB → sine wave pattern → PEA/asystole/VF
  - *ECG does not correlate w/[K^+]*(Clin J Am Soc Neph 2008;3:324)



- Etiologies: **A**cidosis, ↓**A**ldosterone; **B**-blocker, **B**lood; **C**ell lysis/turnover; **D**rugs, **D**M, **D**ecreased GFR
  - **Redistribution**: cell lysis (hemolysis, rhabdo, TLS), acidosis, ↓insulin, hyperosm, meds (digoxin, β-blockers, minoxidil), hyperK periodic paralysis, post-hypothermia
    - Usually transient unless impaired renal K^+ excretion
  - ↓ **Renal K excretion**: required for persistent hyperK^+
    - ↓ Aldo production/action: ACEi/ARBs, NSAIDs, K^+-sparing diuretics, calcineurin inhib, pentamidine, TMP, type IV RTA
    - Impaired Na delivery to distal nephron: hypovolemia, CHF, cirrhosis
    - AKI/CKD (esp. if oliguric): usually GFR<15
    - Other: ureterojejunostomy – urine K^+ reabsorbed
- Management: *acute changes are most dangerous* → **STAT ECG.** Treat if ECG changes, K^+>6, rapid rise, or sx
  - **Elimination is key**, other measures are temporizing. Address reversible factors (optimize volume status, low K^+ diet, meds). Of note, hyperK-related sine waves can be misinterpreted as VT. Do **NOT** use amiodarone if suspected hyperkalemia (deadly)

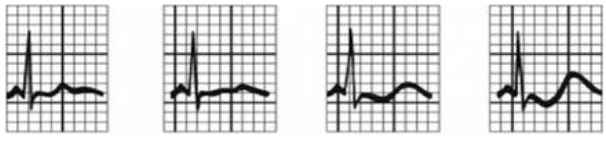
Hyperkalemia Treatment

Strategy	Treatment	Onset	Duration	Notes
Stabilize	**Calcium**: calcium gluconate or $CaCl_2$ (central line) 1-2g IV, can repeat q5 min PRN	1-3m	30-60m	1st line if **any ECG Δs**. Stabilizes cardiac membrane. **Avoid if on dig**
Redistribute	**Bicarb** (sodium bicarbonate 1-2 amps IV vs gtt)	5-10m	1-2h	Drives K^+ into cells. **Consider especially if ↓↓ pH**
	Insulin (5U IV) + **D50** 25g (if BS<250)	10-30m	4-6h	Drives K^+ into cells. ↓K^+ 0.5-1.5mEq/L
	Albuterol (10-20mg neb) (Avoid w/ active ACS or significant tachyarrhythmias)	15-30m	15-90m	
Eliminate	**Furosemide** ≥40mg IV; can approx. as 40xCr if K>6 (Can give with NS to provide volume to diurese)	30m	Variable	Urinary K^+ excretion If ↑↑ volume can + thiazide
	Lokelma (10g TID) > **Patiromer** 8.4 g daily prn (avoid GI binders if SBO/constipation/ileus)	1h; 7h	24h	Swaps K^+ for Ca^{++} or Na^+ in gut
	HD lowers K immediately	N/A	3h	Removes K^+, may rebound d/t shifts

Note: Kayexalate use has ↓↓ in favor of Lokelma given issues w/ efficacy and risk for GI complications (JAMA Intern Med 2019; 179:1023)

Hypokalemia

- Signs and symptoms: usually with K^+<3 → cramps, ileus, weakness (ascending, can involve respiratory muscles), rhabdo, paralysis, worsened HE in cirrhosis (Nat Rev Neph 2010;7:75)
- ECG: flat T waves, ST dep, U waves, ↑QT, atrial or ventricular ectopy → VT, VF (esp if K^+<2.5, susceptible pts, or on digoxin)



- Etiologies:
  - **Lab artifact** (pseudo-hypokalemia): WBC >100 absorb K^+ if sample sits out (check K^+ on blood gas)
  - **Inadequate intake**: unlikely to be 1° cause, usually combined with another etiology
  - **Redistribution**: ↑pH, ↑insulin, refeeding syndrome, ↑β-adrenergic activity (e.g. albuterol, epi), ↑blood cell prod (e.g. s/p G-CSF), hypothermia, toxins (cesium, barium, chloroquine), antipsychotics, hypokalemic or thyrotoxic periodic paralysis
  - **Extrarenal losses**: diarrhea (esp. if chronic, VIPoma, villous adenoma, laxatives), vomiting/NGT
  - **Renal losses** (*w/o HTN*): ↑urine flow (1° polydipsia, excess IVF), ↓Mg, meds (ampho B, ifosphamide, cisplatin, gent)
    - Acidemia: DKA, RTA (proximal [Type II] and some distal [Type I])
    - Alkalemia: diuretics, UGI losses (2° hyperaldo), Bartter's (~loop diuretic), Gitelman's (~thiazide)
    - Other: ↑urine excretion of anions (β-OH-butyrate in DKA, bicarb [e.g. UGI losses], toluene + PCN metabolites)
  - **Renal losses** (*with HTN*):
    - 1° hyperaldo: ↑aldo, ↓renin (e.g. adrenal adenoma); 2°: ↑aldo, ↑renin (e.g. renal artery stenosis, renin-secreting tumor)
    - Other: ↑glucocorticoid or ↑EnaC activity (e.g. Cushing's, Liddle's syndrome, black licorice)
- Management: 10mEq raises K^+ by 0.1mmol/L; caution if ↑Cr or if due to transcellular shifts (e.g. periodic paralysis)
  - Oral KCl (ER = pill, IR = powder) preferred for tx as safer, quick acting, and many pts are Cl^- depleted
  - IV formulation KCl if unable to take PO → max 10mEq/h (floor), 20mEq/h (ICU)
  - Always replete Mg, otherwise K^+ repletion ineffective due to K+ wasting via ROMK (JASN 2007;18:2649)
  - Avoid dextrose-containing solutions → can acutely worsen hypokalemia (dextrose ↑insulin secretion → K^+ shifts into cell)

Samuel Eley

Nephrology Magnesium & Phosphorus Disorders

HYPOMAGNESEMIA (Med Sci (Basel) 2019;7:56)

- S/Sx: lyte disturbances (↓K, ↓Ca), hypoparathyroidism, weakness, delirium, coma, neuromuscular hyperexcitability (e.g. hyperreflexia, tetany, seizures),↑QRS, peaked T waves, later ↑PR, ↑**QTc**, U waves, VT/TdP, accentuation of digoxin toxicity
- Etiologies:
  - **GI**: ↓intake, ↑loss (diarrhea, pancreatitis, malabsorption, small bowel resection, **PPIs**), cellular shift (refeeding syndrome)
  - **Renal**: Meds (thiazide, loop diuretics, amphoB, aminoglycosides, foscarnet, tacro/cyclosporine, cisplatin, digoxin, pentamidine), Gitelman syndrome, EtOH
    - Use **FEMg** to distinguish renal vs GI loss (>3% suggests renal wasting)
- Treatment: oral (slow) vs. IV (fast, typically used inpatient), slow repletion better for sustained correction
  - IV: $MgSO_4$ 1-2g over 2-15min x2 if unstable. If stable, 1-2g over/30min; favor IV if sx, reduce dose if CrCl<30
  - PO: $MgCl_2$ 4-8 tabs/day, causes less diarrhea than Mg oxide 800-1600mg/day, **always use in divided doses**
  - If hypoMg due to thiazide or loop diuretic, can add K-sparing diuretic to decrease Mg excretion

HYPERMAGNESEMIA

- S/Sx (typically only if Mg > 4): nausea, flushing, HA, neuromuscular depression (hyporeflexia [first sign], lethargy, weakness, resp failure), cardiovascular (HoTN, bradycardia, conduction defects [↑PR, ↑QRS, ↑QTc, CHB, arrest]), hypocalcemia (hyperMg can suppress PTH)
- Etiologies: Mg intake > renal clearance. Rarely pathologic w/o renal insufficiency
  - Med overdose (Epsom salts, laxatives, Maalox, Mg enemas) → avoid these agents in ESRD, pre-eclampsia/eclampsia treatment
  - Gastritis/PUD/colitis (increased Mg absorption in these states)
  - Misc - DKA, hypercatabolic states (TLS), lithium, adrenal insufficiency, milk-alkali syndrome
- Treatment (symptomatic only): Ca gluconate 1g IV over 10 min vs gtt to counteract resp depression/cardiac toxicity; **IV fluids** + loop diuretics to enhance renal excretion. If ESRD, HD for removal

HYPOPHOSPHATEMIA

- S/Sx: (typically if phos <1.0 mg/dL, esp. if acute): ↓intracellular ATP →global cellular dysfunction→AMS/encephalopathy, paresthesias, seizures, CHF, resp depression, proximal myopathy, rhabdo, dysphagia/ileus, hemolysis, mineral ∆ (bone pain, hypercalciuria, rickets/osteomalacia) (JASN 2007;18:1999)
- Etiologies:
  - **Redistribution (into cells)**: ↑insulin (DKA, HHNK, **refeeding**), acute resp alkalosis (↑pH → ↑glycolysis), hungry bone syndrome (deposition of Ca and phos in bone immediately following parathyroidectomy)
  - **↓GI absorption**: poor PO, chronic diarrhea, ↓vit D, antacids or phos binders (e.g. aluminum, Mg, sevelamer)
  - **↑Renal excretion**: ↑PTH (1° or 2° hyperPTH), Fanconi syndrome (multiple myeloma, tenofovir), ↑FGF-23 (genetic/paraneoplastic), meds (acetazolamide, metolazone, IV iron) (QJM 2010;103:449), osmotic diuresis (glycosuria), CVVH (esp at high bicarb dose)
  - Use **$FEPO_4$** to distinguish GI/redistribution vs renal (>5% suggests renal wasting)
- Treatment:
  - **Severe** (<1 mg/dL or 1-2 mg/dL and at high risk of becoming severe e.g. refeeding) **or symptomatic**
    - IV Na or K phos 30mmol q6h with frequent levels (can give 15, 30, or 45mmol doses at MGH). Change to PO once >1.5mg/dL. Give ½ dose in CKD/ESRD.
    - Aggressive IV tx can cause Ca precipitation, hypotension (often due to hypocalcemia), AKI, arrhythmia
  - **Asymptomatic** (<2 mg/dL and not at high risk): Na or K phos 1mmol/kg/d PO in 3-4 divided doses (max 80mmol/d)
    - NeutraPhos: 1 packet = 250mg phos (8mmol); 7.1mEq K, 6.9mEq Na; *preferred if need K or want lower Na*
    - K-Phos Neutral: 1 tab = 250mg phos (8mmol); 1.1mEq K, 13 mEq Na
    - If poorly tolerated (can cause diarrhea), can give scheduled skim milk (8oz = 8mmol phos)

ACUTE HYPERPHOSPHATEMIA (for chronic hyperphosphatemia, see *CKD*)

- S/Sx: results from Ca precipitation → hypocalcemia (muscle cramps, tetany, tingling, perioral numbness)
- Etiologies:
  - **Acute phos load** (TLS, rhabdo, exogenous/phosphate-containing laxatives)
  - **Acute extracellular shift** (DKA, lactic acidosis, severe hyperglycemia)
  - **Acute kidney injury** or **CKD** due to decreased clearance (including acute phosphate nephropathy)
  - **Increased tubular reabsorption** (vit D toxicity)
  - **Pseudohyperphosphatemia** (hyperglobulinemia, hyperlipidemia, hyperbilirubinemia, hemolysis)
- Treatment: normal saline (though can worsen hypocalcemia), HD. Consider low phos diet, phos binders (sevelamer), renal consult if refractory/profound

Nephrology IV Fluids & Electrolyte Repletion

IV Fluids (NEJM 2013;369:1243)

- Types: **crystalloid** (e.g. NS or LR), **free water** (e.g. D5W), and **colloid** (e.g. albumin, blood products)
  - Fluids can be isotonic (NS more isotonic than LR), hypotonic (D5W, 1/2 NS, 1/4 NS), or hypertonic (3% saline)
- **Bolus fluids** = volume expansion in distributive/hypovolemic shock, GI losses, burns
  - Rate: 1L over 30min-2h. If concerned about volume overload, start w/ smaller volume (250-500cc).
  - LR has **minor** quantities of K & lactate, ↑K & lactate are **NOT** contraindications to LR (JEM 2018;55:313).
  - NS in large volumes can cause hyperchloremic non-AG metabolic acidosis (NAGMA) and ↑need for RRT (NEJM 2018;378:829; NEJM 2018;378:718) however no Δ mortality when compared to LR (JAMA 2021;326:818). NS likely > LR in ↑ICP (LR is slightly hypotonic and may ↑cerebral edema).
  - Colloid is NOT superior to crystalloid for volume resuscitation in shock (JAMA 2013;310:1809)
- **Maintenance fluids** = goal to replace daily losses (~1.6L/d in adults w/ normal renal function) while preserving electrolyte balance +/- supplying a sugar source. **Always order with time limit.**
  - Rate 60 – 100 mL/h (guided by comorbidities, insensible losses (intubated/burns/fever), oliguria, or ADH excess).
  - D5NS or LR are typical maintenance fluids (NEJM 2015;373:1350). Consider NS in oliguric AKI w/ ↑K (↑distal Na delivery and K excretion) (CJASN 2022;17:588). Consider isotonic bicarb in high output GI fistulas/ostomies.

Fluid	pH	Osm	[Na+]	[Cl-]	[K+]	[Ca^{2+}]	Dextrose	Other/Notes
Human plasma	**7.35-7.45**	**275-295 mOsm/L**	**135-145 mEq/L**	**94-111 mEq/L**	**3.5-5.0 mEq/L**	**2.2-2.6 mg/dL**	**60-100 mg/dL**	**1-2 mEq/L lactate**
Normal Saline (NS)	4.5-7	308	154	154				
Lactated Ringers	6-7.5	281	130	109	4	1.35		29 mEq/L lactate
D5-LR	4-6.5	525	130	109	4	1.35	5 g/dL	29 mEq/L lactate
D5-NS	3.2-6.5	560	154	154			5 g/dL	
1/2 NS	5	154	77	77				
3% NS	5	1026	513	513				See Hyponatremia
D5-1/2 NS	3.5-6.5	406	77	77			5 g/dL	
D5-1/2 NS w/ 20-40KCL	3.5-6.5	426-446	77	97-117	20-40		5 g/dL	
Isotonic NaHCO3	~8	552	150				5 g/dL	=3 amps 50mEq NaHCO3 in 1L D5W
D5W	3.5-6.5	252					5 g/dL	use to correct ↑Na
D10W	3.2-6.5	505					10 g/dL	use w/ insulin gtt
D20W	3.2-6.5	1010					20 g/dL	use w/ insulin gtt

Albumin: MGH Albumin Policy put in place to prevent non-evidence-based overuse (ASA Choosing Wisely)
Albumin 25% = 12.5g albumin in 50mL solution; *Albumin 5%* = 12.5g albumin in 250mL solution
Indications: *use to replace serum oncotic pressure*, not typically for volume resuscitation

- **SBP**: improves renal outcomes. Dosing: 1st dose albumin 25% at 1.5g/kg w/in 6h (max 100g), 2nd dose 1g/kg on Day 3
- **Large volume paracentesis in cirrhosis**: only if >5L removed. Dosing: Albumin 25% at 6-8g/L ascites removed
- **Augmenting diuresis in ARDS**: already on high dose loop diuretic AND albumin <2.5 or Total Prot <6
  Dosing: Albumin 25% at 25g q8h for 3 doses (requires attending approval; stop once alb >2.5. Max 3 days)
- **Hepatorenal syndrome**: see *Hepatorenal Syndrome*
- **Other**: ECMO chatter, mechanical circulatory support, burns, nephrotic syndrome, acute hemorrhagic shock, intra-dialysis
- NOT helpful in decompensated cirrhosis unless for the above indications (NEJM 2021;384:808)

Electrolyte Repletion

	Potassium	Magnesium	Phosphorus	Calcium
Goal and Route	- CAD/arrhythmia: ≥4 - Everyone else: ≥3.5 - Do not replete if on HD unless <3.0 **PO > IV**	- CAD/arrhythmia: ≥2 - Everyone else ≥1.7 **IV > PO**	- Replete if phos <2 **PO preferred** **IV if <1 or <1.5 + symptoms** Symptoms: weakness, MKS pain, SOB/resp failure, CHF, Δ neuro	- Replete if sx, long QTc, Ca <7.5, iCal <1.15mmol/L **PO > IV unless iCal <1.0**
PO repletion	- KCl IR (powder): q4-6h - KCl ER (pills): giant pills - If K <3.5, ≥20 mEq KCl IR - see Lexicomp for dosing	- Mg oxide 400mg (240mg elemental Mg) TID x1d	- Phos-Nak: 1 packet QID (7 mEq K, 7 mEq Na) - K-Phos-Neutral: 1 packet QID (1 mEq K, 13 mEq Na)	- Ca carbonate 1250mg PO BID
IV repletion	- Peripheral: 10mEq/h - Central: 20mEq/h w/ telemetry monitoring	- Mg sulfate 2g IV	Give 15-45mmol Phos over 6 hr - K-Phos (1.5mEq K/mmol Phos) - Na-Phos (1.3mEq Na/mmol Phos)	- Ca gluconate 1-2g IV; - $CaCl_2$ used in codes, 0.5-1g q2-5min
Comments	- **10mEq K ↑serum K by 0.1 (in normal kidney function)** - re-check K every 40mEq unless on stable daily dose - **Correct hypoMg**	- **2g ↑serum Mg by 0.5** - ↓Mg can cause ↓K/Ca	- IV Phosphate can precipitate Ca → causing hypocalcemia - **Reduce/halve dose in CKD**	- Correct for low Alb & hyperphos first - **1g Ca gluconate ↑serum Ca by 0.5**

Nephrology Urinalysis & Nephrolithiasis

URINALYSIS

URINE DIPSTICK – urine should be analyzed within 2-4h

Specific Gravity	Can help approximate urine osm: decimal of SG x 30 (e.g. SG 1.020 → 20 x 30 → ~ 600mosms) **SG <1.010**: post-ATN (concentrating defect), diuretics, DI, polydipsia, hypovolemic hypoNa *after resuscitation* **SG 1.010 – 1.025**: normal; **SG >1.025**: prerenal, contrast (esp >1.030), ↓EABV, glycosuria (DM), proteinuria, SIADH
pH	Normal 4.5 - 8, but strongly depends on serum pH and dietary intake If normal urine pH + metabolic acidosis, suspect type I RTA (kidney not secreting H^+ ions) If pH ≥7, suspect urease-producing organisms (Proteus, PsA), strict vegetarians (low protein diet), type I RTA
LE	Released from lysed PMNs; **FP**: ↓pH or ↓SG (lyses WBCs); **FN**: proteinuria, glycosuria. For UTI, **Sn 80%, Sp low**
Nitrite	Indicates nitrate-reducing GNR (E. coli, Klebsiella, Proteus, PsA – NOT Enterococcus). For UTI, **Sn 60%, Sp>90%**
WBC	UTI; if sterile pyuria, consider AIN, GN, chlamydia, ureaplasma, urethritis, TB, foreign body, exercise, steroids
Blood	Detects heme (glomerular, renal, or urologic); **FP**: hemoglobinuria (hemolysis), myoglobinuria (rhabdo), semen, drugs (rifampin, chloroquine, iodine), peroxidase producing bacteria
Protein	Only detects albumin, not LMW proteins or light chains. + Protein when excretion >300mg/d. Falsely elevated by high SG, heavy hematuria (heme protein), and iodinated contrast (w/in 24h)
Ketones	Detects only acetoacetate, NOT β-hydroxybutyrate; yield decreases as collected urine sits
Glucose	Reflects glomerular overflow (serum glucose >180mg/dL or SGLT-inhibitor/mutation) OR PCT failure (glycosuria w/ normal serum glucose → consider Fanconi's syndrome 2/2 MM, heavy metal, drugs, etc.)

URINE SEDIMENT (MICROSCOPY)

- Urine microscopy room: to the left of Harris room, outside White 10
- Nephrology fellow/attending (day) or Security (night) can let you in
  1. Obtain 10cc of **fresh urine**
  2. **Centrifuge** using a balance @ 3000 RPM x3-5min
  3. **Invert/drain supernatant** and **resuspend** sediment in the few drops of urine that remain in the tube. Place one drop of sample on slide and place coverslip.
  4. Bright Field Microscopy: keep light source subdued, lower condenser to maximize contrast, start at **low power** (10x) to obtain a general impression. Pay attention to **coverslip edge** where casts tend to migrate.
  5. **Phase contrast microscopy:** maximizes contrast and definition, allows better visualization of casts and cells. Raise condenser up high and turn light source to maximum brightness. Objective and condenser annulus should always match.

Findings	Description
RBCs	Glomerular (dysmorphic RBCs "mickey mouse ears") vs non-glomerular (normal). If present, can require outpt repeat with timing based on #RBCs and risk factors
WBCs	UTI/cystitis (>10/microL expected for true infxn), pyelonephritis, AIN, atheroembolic, glomerular injury, renal/bladder TB, stones
Epithelial Cells	Tubular (ATN), transitional (proximal urethra to renal pelvis), squamous (contamination by genital secretions)
Casts	Viewed best w phase contrast: Hyaline, RBC, WBC, Muddy brown, Granular, Waxy, Fatty
Crystals	Viewed best w phase contrast: Acyclovir ("needles"), Tenofovir, Struvite ($NH_4 \cdot Mg \cdot PO_4$), ethylene glycol (oxalate)

CONDITION	UA	CELLS	CASTS/CRYSTALS	COMMENTS
Pre-renal azotemia	SG >1.010		Hyaline, granular	↓FENa (if oliguric), ↓FEUrea
Nephrotic syndrome	3+ protein		Oval fat bodies, hyaline	
Glomerulonephritis	+ heme, +protein	Dysmorphic RBCs	RBC casts, WBC, granular	
ATN	SG ~ 1.010 ("isosthenuria")	Hallmarks: renal tubular epithelial cells (RTECs) and muddy casts (CJASN 2008;3:1615) PPV for ATN ~100% if ↑pre-test prob and any RTECs and/or muddy casts present.		
Rhabdomyolysis, hemolysis	3+ heme w/o RBCs on sediment	NO cells	Acellular hyaline casts with red or brown pigmentation	↓FENa, red/brown urine
AIN	Sterile pyuria	WBCs	WBC casts, granular	Urine eos NOT sens or spec
Renal infarct	Sterile pyuria	+ RBCs, WBCs		↑urine LDH (↑serum LDH)
Cholesterol emboli	Sterile pyuria		Cholesterol	
Myeloma kidney		Bland	Bland	Proteinuria NOT detected by UA
CKD			Waxy	± impaired ability to concentrate

NEPHROLITHIASIS

Composition and prevalence: CaOxylate > CaPhosphate > Urate = Struvite > Cysteine
Risk factors: male, obesity, DM, white, southeastern US, oral antibiotics, CKD, ESRD, family history (2% attributed to inherited disease)
Workup: CT (I-) > US (urological procedures require CT for planning). Can strain urine to type stone. Can also get 24h urine ("Litholink") at home both before and after interventions (usually dietary) are made
Precipitating factors: low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, hypomagnesuria, hypercystinuria, urea splitting bacteria, high sodium intake, acidic urine (urate, cysteine), or basic urine (calcium phosphate, struvite), drug-induced (guaifenesin, triamterene, sulfa drugs, protease inhibitors), toxic ingestion (ethylene glycol → Ca oxalate stones)
Acute management: IVF, pain management (ketorolac preferred to opioids) alpha blockers (>5 mm); urologic intervention if >10mm, concern for infected stone, AKI, unremitting pain/n/v, or anuria. See: Ureteral obstruction. See AAFP algorithm (Am Fam Phy 2019;99:490)
Chronic management: fluid intake >2.5L/d, low Na diet, high K diet, low oxalate diet (no nuts, chocolate, green leafy veggies, etc.), increase Ca intake, avoid excess vitamin D, thiazide diuretics if calcium stones, allopurinol if hyperuricosuria
Citrate supplementation: used for inhibition of Ca and uric acid stone formation. Leads to metabolic alkalosis. ↓new stones, stone size

Infectious Disease Empiric Antibiotics & Antibiogram

PRINCIPLES OF ANTIBIOTIC SELECTION (IDSA Guidelines, Sanford Guide, Johns Hopkins Abx Guide)

Consider the *substrate*:

- Is the patient **immunocompromised**? Think about age, DM, medications (≥ 20 mg prednisone QD x 2 weeks), HIV, neutropenia, ESLD, ESRD.
- Is the patient **at risk** for any particular kind of infection? Think about prostheses, lines, altered anatomy, behaviors, and recent hospitalizations.

Consider the *tempo/severity*:

- Is the patient **unstable**? If so, start broad spectrum antibiotics quickly; *time to antibiotics correlates with mortality in septic shock.*

Consider the *syndrome:*

- What **evidence** is there of infection? *e.g.,* fever, localizing symptoms, leukocytosis, hypotension, inflammatory markers
- What is the likely **source**? *e.g.,* PNA, UTI, SSTI, bone & joint infection, CLABSI, GI
- If a source is evident, what are the **most common pathogens**?
- Might there be **metastatic foci of infection**? *e.g.,* blood, CSF, valves, bones, joints

Other considerations:

- If safe, **cultures before antibiotics** to improve diagnostic yield.
- Review the patient's **prior microbiology** to assess for history of resistant bugs
- **Broader ≠ better**. We routinely overcover for MRSA, *Pseudomonas*, and anaerobes.
- **Longer ≠ better**. Emerging studies show shorter duration is noninferior in a number of infections.
- **Fever ≠ infection.** Don't forget to consider inflammation, thrombus, medications, *etc.*
- **Narrow** and **convert to PO** when able (if indicated). Use the *MGH antibiogram* and, eventually, the *susceptibility report*.
- **Inadequate source control** is a common cause of treatment failure. Remove the line, drain the abscess, etc.

Antibiotic pharmacokinetic properties:

- High **CNS penetration** *(not exhaustive)***:** PCN, ampicillin, nafcillin, CTX, imipenem, mero, metronidazole, doxy (Lyme only), linezolid. Vanc is moderate but improves with severe meningeal inflammation. MGH Antibiotic penetration tip-sheet
- High **oral bioavailability** (*i.e.*, PO=IV) *(not exhaustive)*: metronidazole, linezolid, doxy, FQs, azithro, clindamycin
- High **urinary accumulation** (*not exhaustive*): PCN, amoxicillin, cefazolin, cipro, aminoglycosides, vancomycin

Additional resources:

- For up to date MGH Antibiogram & Guidelines for Empiric Therapy for Inpatients: click (VPN or hospital WiFi) & scroll down
- Surviving Sepsis Campaign – 2021 Adult Guidelines

General spectrum of coverage for common IV β-lactams

Gram positives	*Gram negatives*	*Anaerobes*	*Pseudomonas*
penicillin / cefazolin			
ampicillin			
ceftriaxone / cefotaxime			
cefepime			
ampicillin-sulbactam			
piperacillin-tazobactam / meropenem			

Commonly encountered Bugs & Drugs

Microbe	Antibiotics	Notes
Staphylococcus aureus	MSSA: IV nafcillin, cefazolin, oxacillin PO cephalexin, cefadroxil	-Cefadroxil is BID, cephalexin is QID -β-lactam >>>> vancomycin
	MRSA: IV vancomycin, daptomycin, ceftaroline PO doxy, TMP-SMX, LZD, clinda Long-acting dalbavancin, oritavancin	-Dapto is inactivated in lung by surfactant -LZD highly bioavailable if PO and well tolerated for short course (<2wk)
Group A streptococci	-penicillins	-Add clinda if concern for TSS
Enterococci	-ampicillin, vancomycin, daptomycin, linezolid -fosfomycin, nitrofurantoin (UTI only)	-MGH antibiogram shows good *E. faecalis* susceptibility to ampicillin -If *E faecium*, more likely to harbor resistance
Pseudomonas aeruginosa	-IV cefepime, ceftazidime, piperacillin-tazobactam, imipenem, meropenem, aminoglycosides -PO ciprofloxacin, levofloxacin	-Ertapenem does not cover PsA -MGH defines resistant PsA as R to ceftaz and may need ID guidance for abx choice
MDR GNRs (AmpC inducers and ESBL producers)	-IV cefepime, carbapenems, aminoglycosides -PO fluoroquinolone, TMP-SMX	-AmpC: *Enterobacter, Serratia, Providencia, Proteus* (indole+), *Morganella, Citrobacter* -Cefepime success highly-dependent on MIC
Cell wall-deficient ("atypicals")	-doxycycline, azithromycin, levofloxacin	*-Mycoplasma, Chlamydia*, *Legionella*
Anaerobes	-IV pip-tazo, amp-sulbactam, carbapenems -PO metronidazole, clinda, amox-clav	-Think twice if anerobic coverage needed -Vanc+cefe does NOT cover anaerobes

Infectious Disease Empiric Antibiotics & Antibiogram

Suspected Process	Microbiology	Empiric Antimicrobial Therapy	Notes
Meningitis (CID 2004;39:1267; CID 2017;64:e34)	-Generally: *S. pneumoniae*, HSV, other viral > *N. meningitidis* -If >50 y, immunocompromised, EtOH: *Listeria monocytogenes* -If hardware or nosocomial: Staph, PsA; *C. acnes* if VP shunt	-vancomycin+ CTX 2g Q12 -*Listeria*: ampicillin -HSV: acyclovir -Healthcare-assoc, hardware, VP shunt, PWID: vancomycin + cefepime or meropenem	-If *S. pneumoniae*, add dexamethasone (reduces neurologic sequelae) -Remove hardware if possible (*e.g.,* place external ventricular catheter in place of shunt) -See Abx penetration tip sheet
Community Acquired Pneumonia (CAP) (AJRCCM 2019;200:e45)	-viral > bacterial -*Legionella*, *Mycoplasma*, *Chlamydia* ("atypical") -*S. pneumoniae* (classic lobar PNA), *H. influenzae*, *Moraxella catarrhalis* -*S aureus* (usually very sick) -*Klebsiella* (EtOH)	-Healthy outpt: amox > azithromycin or doxy -Outpt with comorbidities: Amox-clav+azithro or doxy, cefpodoxime+azithro or doxy, or levoflox alone -Most inpatients: CTX+azithro, or levo alone -Prior MRSA/PsA OR IV abx in past 90 d: vancomycin+cefepime+azithromycin	-Recommend flu and viral testing -Consider local azithromycin resistance -Can substitute doxycycline for azithro -Levofloxacin preferred for structural lung disease outpatient -If postviral, consider *S aureus* -If empyema, **needs drainage**
Hospital-Acquired and Ventilator-Associated Pneumonia (HAP/VAP) (CID 2016;63:e61)	-CAP organisms, *S aureus*, GNRs including PsA, *Stenotrophomonas*	-vancomycin+cefepime	-Consider local MDRO prevalence
Endocarditis (Circ 2015;132:1435)	-Native: *S aureus*, strep, enterococci, few GNRs, HACEK -Prosthetic: *S aureus*, *S. epidermidis* most likely; others above rarely	-Native: vancomycin+ceftriaxone -Prosthetic: vancomycin+gentamicin+rifampin, but ask ID	-Early ID consult improves mortality and can help guide empiric therapy early based on patient characteristics!! -MSSA: β-lactam >>> vancomycin
Cholecystitis/ Cholangitis (CID 2010;50:133)	-*E. coli*, *Klebsiella*, enterococci, anaerobes -Often polymicrobial	-CTX+MNZ, cipro+MNZ -Nosocomial/severe: cefepime+MNZ, piperacillin-tazobactam, imipenem, meropenem	-Source control: CCY, ERCP, or perc choly -Consider vancomycin if c/f enterococci -Often polymicrobial → broad abx for 48 h even if BCx growing only 1 organism
Other Intra-abdominal (CID 2010;50:133)	-Abscess: GNRs, anaerobes, enterococci, *Candida*, polymicrobial -Diverticulitis: GNRs, anaerobes, rarely enterococci, polymicrobial	-CTX+MNZ, ciprofloxacin+MNZ -Nosocomial/severe: cefepime+MNZ, piperacillin-tazobactam, imipenem, meropenem	-Drain if abscess -Surgical evaluation if peritonitis, perforation, fistula, recurrent diverticulitis
Spontaneous Bacterial Peritonitis (SBP) (Hep 2021;74:1014)	-Enteric GNR, streptococci, enterococci; rarely anaerobes	-ceftriaxone, cefotaxime	-Ciprofloxacin reserved for patients w/ β-lactam allergies and used for ppx -Initiate ppx after first episode of SBP
UTI (non-pregnant) (CID 2011;52:e103; CID 2010;50:625)	-Uncomplicated: *E.coli*, *Klebsiella*, *S. saprophyticus*, *Proteus* -Complicated (*i.e.* systemic infxn, pyelo): above + enterococci, PsA, *Serratia, Providentia* -CAUTI: above + other GNRs	-Uncomplicated: nitrofurantoin, TMP-SMX, fosfomycin -Complicated: CTX, ciprofloxacin/levofloxacin -CAUTI: vancomycin+ceftriaxone -Cefepime if c/f PsA, carbapenem if c/f ESBL	-Do not treat asymptomatic bacteruria in nonpregnant immunocompetent patients -Exchange Foley, consider repeat UA/UCx 48 h later if CAUTI
Osteomyelitis (CID 2023;ciad527; CID 2015;61:e26)	-Hematogenous source: *S aureus* -Direct inoculation/vascular: *S aureus* > strep, PsA, GNR, enterococci, *Eikenella* (human bite), *Pasteurella* (animal bite)	-No abx if HDS, no signs c/f cord compression, and awaiting bone biopsy -Vanc+CTX; cefepime if DM/PAD ulcer or direct inoculation	-Dx: CRP, ESR, MRI, bone biopsy -Debride (ortho/vasc surg/plastics) w/ bone bx+cx -Use amp-sulbactam if originated from bite
Septic Arthritis (Infect Dis Clin North Am 2017;31:203)	-staph, strep, *N. gonorrhoeae*, PsA (PWID), Lyme	-vancomycin+ceftriaxone (consider cefepime if PWID or other risk factor for PsA) -Definitive rx is a joint wash out	-Dx: fluid aspirate with >50k WBC -Consult ortho for joint washout asap -Blood+joint fluid cx prior to abx
Skin/Soft Tissue (SSTI) (CID 2014;59:e10)	-Impetigo: *S aureus* > strep -Cellulitis/Erysipelas: strep > staph -Nec fasc: strep, *C. perfringens*, MRSA	-Purulent: vancomycin -Non-purulent: cefazolin -Bite: ampicillin-sulbactam -Nec fasc: vanc+ [pip-tazo or mero] ±clinda -DM/PAD ulcer: vanc + [CTX or cefe]	-If abscess, drain -If nec fasc (rapid spread, crepitus, pain out of proportion), URGENT SURGICAL EVAL -If nec fasc, clinda meant to inhibit exotoxin production
Septic shock, no source (Intensive Care Med 2021;47:1181)	-GNRs, *S aureus,* streptococci, PsA, anaerobes -Consider TSS	-vanc+cefe±MNZ, vanc+pip-tazo -Concern for MDRO: carbapenem -Critical illness: consider 1 dose aminoglycoside -TSS: add clindamycin	-Start antibiotics within 1 h of recognition -Amikacin generally the aminoglycoside of choice for critical illness
Febrile Neutropenia (T≥100.4F & ANC<500) (CID 2011;52:e56)	-Source not identified ~70% of time -When source is identified, 60% GPCs (CoNS > *S aureus*, streptococci, enterococci), 40% GNRs (*E. coli*, *Klebsiella* > PsA)	-cefepime -Suspect CLABSI, SSTI, PNA, mucositis: add vancomycin -HDUS, GPCs on BCx: add vancomycin -Persistent fevers > 4-7 d: consider micafungin	-Start antibiotics within 1 h of fever -If afebrile x 72 h or ANC > 500, consider de-escalation -Oral ppx: consider levo or amox-clav + cipro for prolonged neutropenia

Bacterium	No. of Strains	% SUSCEPTIBLE														
		Penicillin	Ampicillin	Oxacillin	Cefazolin	Ceftriaxone	Vancomycin	Clindamycin	Erythromycin	Doxycycline	TMP - SMX	Levofloxacin	Linezolid	Daptomycin	Rifampin[a]	Nitrofurantoin[b]
Staphylococcus aureus	3566	-	-	72	SP[c]	-	99	73	52	97	92	81[d]	100	99	99	99
Coagulase-negative staphylococci	2093	-	-	51	SP[c]	-	100	60	40	86	66	69[d]	99	99	94	99
Staphylococcus lugdunensis	391	-	-	92	SP[c]	-	100	82	80	99	99	97[d]	100	100	99	99
Staphylococcus saprophyticus	187	-	-	-	-	-	100	-	-	99	98	100[d]	100	-	100	100
Streptococcus pneumoniae (non-meningitis)	102	99	-	-	-	99	100	82	61	54[e]	80	100	-	0	-	-
Streptococcus pneumoniae (meningitis)		76	-			89										
β-hemolytic streptococci (group A)	319	100	SP[f]	-	SP[g]	100	100	77	75	54[e]	-	98	-	-	-	-
β-hemolytic streptococci (group B)	1089	100	SP[f]	-	SP[g]	100	100	56	51	16[e]	-	99	-	-	-	-
β-hemolytic streptococci (group C, G)	140	100	SP[f]	-	SP[g]	100	100	61	60	51[e]	-	98	-	-	-	-
α-hemolytic streptococci[h]	361	53	-	-	-	92	100	88	44	64[e]	-	92	-	-	-	-
Streptococcus anginosus (*milleri*) group	361	97	-	-	-	100	100	80	73	62[e]	-	99	-	-	-	-
Enterococcus avium	64	-	95	0	R	R	100	R	66	41	R	92[d]	100	-	-	42
Enterococcus casseliflavus[i]	26	-	100	0	R	R	R	R	27	92	R	96[d]	100	-	-	100
Enterococcus faecalis[i]	2161	-	100	0	R	R	92	R	12	29	R	82[d]	99	99	-	99
Enterococcus faecium[k]	579	-	18	0	R	R	40	R	7	37	R	16[d]	99	95[l]	-	18
Enterococcus gallinarum	34	-	100	0	R	R	R	R	85	65	R	91[d]	100	-	-	100

Abbreviation: SP, susceptibilities inferred from another agent; R, intrinsic resistance.
Symbols: (-) Drug not tested or insufficient data available.
[a] Rifampin should not be used alone for therapy.
[b] Urine isolates only.
[c] For staphylococci, Cefazolin is predicted from oxacillin.
[d] For serious infections from staphylococci or enterococci, levofloxacin should not be used alone for therapy.
[e] For streptococci, rates are tetracycline susceptibility rates.
[f] For β-hemolytic streptococci, ampicillin is predicted from penicillin.
[g] For β-hemolytic streptococci, Cefazolin is predicted from penicillin.
[h] Includes alpha-hemolytic streptococci, *S. bovis*, *S. mitis*, *S. mutans*, *S. oralis*, *S. parasanguinis*, *S. pseudopneumoniae*, *S. salivarius*, *S. sanguinis*, *S. vestibularis*.
[i] Calculated from fewer than the standard recommendation of 30 isolates, reducing statistical validity.
[j] 13% high-level resistance to gentamicin; streptomycin not routinely tested but available on request.
[k] 5% high-level resistance to gentamicin; streptomycin not routinely tested but available on request.
[l] Only198 isolates tested. See "Antimicrobial Costs" table for information about the need for higher daptomycin dosing in *E. faecium* infections.

Yeast	No. of Strains	Fluconazole (% susceptible)
Candida albicans	449	98
*Candida glabrata**	124	93
Candida parapsilosis	77	100
Candida tropicalis	37	95

Note: Candida krusei are intrinsically resistant to fluconazole.

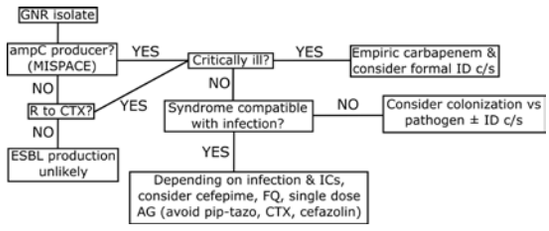
* See "Antimicrobial Costs" table for information about the need for higher fluconazole dosing in *C. glabrata* infections.

Bacterium	No. of Strains	% SUSCEPTIBLE														
		Ampicillin	Amoxicillin-Clavulanate	Piperacillin-Tazobactam	Ceftriaxone	Ceftazidime	Cefepime	Ertapenem	Meropenem	Gentamicin	Amikacin	Ciprofloxacin	Levofloxacin	TMP – SMX	Tetracycline	Nitrofurantoin[a]
Achromobacter spp.	76	-	-	91	-	75	18	-	82	0	0	19	50	84	16	-
Acinetobacter baumannii complex[b]	127	R	R	72	0	62	79	R	89	89	-	81	84	85	77	-
Aeromonas spp.[c]	28	R	R	93	93	-	93	93	93	96	100	93	-	86	-	-
Burkholderia spp.	34	0	0	0	0	59	0	0	84	0	0	-	65	84	-	-
Citrobacter freundii complex	306	R	R	82[d,e]	77[e]	-	97	96	99	93	100	88	84	87	85	93
Citrobacter koseri (diversus)	180	R	98	99[e]	98	-	100	100	100	99	99	98	98	99	97	96
Enterobacter cloacae complex	666	R	R	76[d,e]	71[e]	-	91	88	99	95	99	89	86	87	86	51
Escherichia coli[f]	6871	51	82	95[g]	87	-	96	99	99	89	99	75	70	71	71	97
Hafnia spp.	42	R	R	37[d]	81	-	98	98	100	100	100	100	100	100	69	100
Klebsiella (not identified to species)	151	R	86	95[g]	91	-	98	99	99	96	100	87	86	95	92	70
Klebsiella (Enterobacter) aerogenes	212	R	R	80[d,e]	78[e]	-	97	97	99	100	100	96	90	98	91	22
Klebsiella oxytoca	413	R	90	91[g]	94	-	98	99	99	98	99	95	95	95	94	92
Klebsiella pneumoniae[f]	1891	R	85	89[g]	80	-	91	98	99	90	99	77	73	79	74	28
Morganella morganii	248	R	R	98[g]	88	-	95	99	99	93	100	88	88	80	59	R
Proteus mirabilis[f]	900	77	≥77[h]	99[g]	98	-	98	99[h]	100	93	99	83	83	81	R	R
Proteus vulgaris	69	R	-	100[g]	90	-	99	97[h]	100	100	100	93	93	84	R	R
Providencia rettgeri	50	R	R	93[d]	94	-	92	94[h]	100	100	100	88	79	92	R	R
Providencia stuartii	40	R	R	97[g]	90	-	93	95[h]	100	R	100	40	23	90	R	R
Pseudomonas aeruginosa[i]	1459	R	R	74[j]	R	84	86	R	85	-	93	80	67	R	R	R
Raoultella spp.	76	R	92	100[g]	88	-	96	100	100	89	100	89	91	86	76	97
Salmonella spp.	74	96	99	100[g]	97	-	100	100	100	0	0	62	61	99	89	-
Serratia marcescens	327	R	R	-	97	-	98	98	99	98	100	91	89	98	25	R
Shigella spp.[k]	17	24	53	100[g]	65	-	100	100	100	0	0	47	29	24	6	-
Stenotrophomonas maltophilia[k]	323	R	R	R	R	31	0	R	R	R	R	-	84	98	R	-

Abbreviation: R, intrinsic resistance; SDD, susceptible dose dependent.
Symbols: (-) Drug not tested or insufficient data available.
[a] Urine isolates only.
[b] For *A. baumannii* complex, 91% are susceptible to ampicillin-sulbactam.
[c] Calculated from fewer than the standard recommendation of 30 isolates, reducing statistical validity.
[d] % based on data from February-December 2023 and includes SDD isolates.
[e] Third generation cephalosporins and piperacillin-tazobactam should be avoided for non urinary or moderate to severe systemic infections with these organisms because resistance may emerge during treatment.
[f] For the treatment of uncomplicated UTI with cefazolin: for *E. coli* (1623/1951) 83% are susceptible, for *K. pneumoniae* (326/439) 74% are susceptible, for *P. mirabilis* (217/223) 97% are susceptible when 1g of cefazolin is administered IV every 12 hours. It also predicts susceptibility for the oral agents cephalexin, cefadroxil, and cefpodoxime.
[g] Due to internal reporting rules, results obtained for amoxicillin clavulanate are not available for all isolates tested. The %S statistic is predicted from ampicillin and assumes that additional untested isolates are likely susceptible to amoxicillin-clavulanate, however, the exact number of additional susceptible isolates is unknown.
[h] Due to internal reporting rules, results obtained for ertapenem are not available for all isolates tested. The %S statistic is an adjusted estimate of %S based on the data available and an assumption that untested isolates are susceptible.
[i] For *P. aeruginosa*, 95% are susceptible to tobramycin.
[j] Only 129 isolates tested.
[k] *S. maltophilia* (26/28) 93% isolated tested are susceptible to minocycline.

MDR GNRs (CID 2023;ciad:428)

AmpC β-Lactamase (cephalosporinase)



- Mechanism: Inactivate 3rd gen cephalosporins & pip-tazo. Can be constitutive or inducible (turned on by accumulation of cell wall fragments due to β-lactam inhibition of penicillin-binding proteins).
- Pathogens: Inducible AmpC producers include:
  MISPACE: ***M****organella spp.*, **I**ndole-positive *Proteus spp.* (non-*mirabilis*), ***S****erratia spp.*, ***P****rovidencia spp.*, ***A****cinetobacter spp.*, ***C****itrobacter spp.*, ***E****nterobacter spp.*
  HECKYes*:* ***H****afnia alvei,* ***E****nterobacter cloacae,* ***C****itrobacter freundii,* ***K****lebsiella aerogenes,* ***Y****ersinia enterocolitica*
  - Organisms don't equally produce AmpC; *E. cloacae*, *K. aerogenes* (formerly *E. aerogenes*), & *C. freundii* are highest risk (CID 2021;74:2089).
- Treatment**:** Do not treat these organisms with 3rd gen ceph (*e.g.,* CTX), even if the micro lab report says "susceptible."
  - If critically ill, treat with ***cefepime*** if MIC ≤ 2 µg/mL. Generally, cefepime noninferior to meropenem (CID 2013;57:781).
  - If not critically ill, can de-escalate to alternatives (*e.g.,* FQ, TMP-SMX, or nitrofurantoin [only cystitis]) if susceptible.

Extended-Spectrum Beta Lactamases (ESBL)

- Mechanism: Plasmid-mediated, inactivate most β-lactams (penicillins, cephalosporins, aztreonam).
- Pathogens: *Klebsiella spp.* (#1), *E. coli* (#2), *Proteus mirabilis* (#3), other GNR
- Risk Factors: Abx w/in past 6 mo, long hospitalization, nursing home, >65 yo, lines/catheter/tubes/ventilator, TPN, HD
- Laboratory detection: MGH infection control defines potential ESBL as a GNR resistant to ceftriaxone.
- Treatment: Avoid penicillins and cephalosporins (including piperacillin-tazobactam) even if "susceptible" (JAMA 2018;320:984)
  - *Uncomplicated cystitis* = ***TMP-SMX*** or ***nitrofurantoin***; alternatives: Fosfomycin (E.Coli), single-dose aminoglycoside. Cipro/levoflox or carbapenem are last line. *Complicated UTI*: ***TMP-SMX*** *or* ***FQ***; alternative: Carbapenems
  - If non-UTI, empiric treatment with ***imipenem-cilastatin*** or ***meropenem***. Avoid ertapenem in critical illness.

Carbapenem Resistant Enterobacteriaceae (CRE)

- Mechanisms: Inactivating carbapenemase, porin loss (limits penem entry), efflux pump extrusion, or combination of factors
- Risk Factors: Cephalosporin or carbapenem use in past 3mo (**penem exposure not required**), medical care in India/Pakistan
- Laboratory detection: Suspicious when MIC > 2 µg/mL for imipenem, meropenem, or ertapenem
- Treatment: Preferred option is usually ***ceftazidime-avibactam*** (+aztreonam if care in India/Pakistan); **C/s ID**
  - Meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are also active
  - Alternatives may include extended-infusion meropenem (if MIC ≤ 1 µg/mL), aminoglycoside, or tigecycline [not for UTI/bacteremia]**.**
  - If uncomplicated UTI – FQ, TMP-SMX, or single-dose aminoglycoside if susceptible.

Difficult-to-Treat Resistance *Pseudomonas aeruginosa* (DTR-PsA)

- Definition: Non-susceptible to pip-tazo, ceftaz, cefepime, aztreonam, fluoroquinolone, meropenem, AND imipenem-cilastatin
- Treatment: ***Ceftolozane-tazobactam*** usually preferred but other options (e.g. ceftaz-avibactam, cefiderocol, etc.); **C/s ID**

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

Community-associated MRSA: no healthcare exposure, SSTI in young & healthy patient

- Risk Factors: HIV, PWID, prior antibiotic use; outbreaks: incarceration, military, sports, sharing needles/razors

Healthcare-associated MRSA: occurs >48h following hospitalization or within 12mo of healthcare exposure

- Risk Factors: recent hospitalization/surgery, HD, LTC facility residence
- Nasal swab: NPV in CAP = 96.5% (CID 2018;18:1) if ⊖ consider d/c MRSA coverage. MGH use Antimicrobial De-escalation Guidelines in HAP/VAP; emerging evidence that NPV for Staph infection at other sites is also high (CID 2020;71:1142).

Treatment

- Check the vanc MIC: Vanc susceptible if MIC ≤2 µg/mL (though ↑tx failure and mortality when MIC = 2 µg/mL), Vanc-intermediate (VISA) if 4 µg/mL ≤ MIC ≤ 8 µg/mL, Vanc-resistant (VRSA) if MIC ≥16 µg/mL
- Serious infections (*i.e.* bacteremia): **vancomycin** (consider AUC dosing, trough ~15-20) and **ID consult** (J infect. 2016;72:19). If persistent bacteremia or MIC ≥ 2 µg/mL, consider switching to **daptomycin** (**not in PNA** or meningitis), adding ceftaroline (Antimicrob Agents Chemother. 2018;62:01554), or both (Open Forum Infect Dis 2019;7:538).
- Mild infections (*e.g.,* SSTI): TMP-SMX, doxycycline >> clindamycin (increased resistance at MGH); linezolid

VANCOMYCIN RESISTANT ENTEROCOCCI (VRE)

- *E. faecium*: often resistant & generally less virulent. *E. faecalis*: more virulent but highly Amp^S at MGH.
- RFs: prior abx, Foley, indwelling lines; proximity to other VRE pts; long hospitalization/SNF; immunocompromised
- Clinical sites of infection: UTI (often an **asymptomatic colonizer**); bacteremia (2nd most common CLABSI); intra-abdominal and pelvic infections; endocarditis (esp. if prosthetic valve); meningitis (immunocompromised or VP shunt)
- Treatment:
  - Invasive infection (*e.g.,* bacteremia, endocarditis): daptomycin (+ amp or CTX or ceftaroline), linezolid; **ID c/s**
  - Uncomplicated UTI: fosfomycin x1 (consider repeat dose on days 4 and 7) or nitrofurantoin

COMMUNITY ACQUIRED PNEUMONIA (CAP) (AJRCCM 2019;200:45)

- **Definition**: PNA acquired in the community, including patients from nursing homes, dialysis, or with outpatient clinic exposure
- **Diagnosis**: new infiltrate on chest imaging AND s/sx (e.g. fever, cough, leukocytosis, Δ sputum, hypoxemia)
  - Elderly at ↑risk of blunted s/sx but also ↑prevalence of atelectasis/aspiration
  - Radiographic consolidation NOT specific for bacterial vs viral PNA
  - If CXR ⊖ but high suspicion → tx and repeat CXR in 24h (PNA may "blossom") vs. consider chest CT → if ⊖ consider other dx
- **Triage**: CURB-65 (Confusion, BUN>19, RR>29, BP<90/60, age≥65) → outpatient if score 0-1, inpatient if 2, consider ICU if 3-5. Pneumonia Severity Index (PSI) more comprehensive → outpatient if <70, inpatient if >90
- **Severe CAP (ATS/IDSA Criteria)**: **1 Major**: pressors or mech vent, OR **3 Minor**: RR≥30, P:F≤250, multilobar infiltrates, confusion, BUN>19, WBC<4K (not due to chemo), plt<100K, T<36C, HoTN requiring aggressive fluid resuscitation
- **Micro**: S. aureus (common in severe CAP), S. pneumoniae, H. flu, GNRs, Legionella. Most common pathogens are viruses – rhinovirus, influenza, others (NEJM 2015;358:415; CritCareMed 2022;50(7))
- **Work-up (inpatient)**:
  - **Sputum cx and Gram stain** (ET aspirate if intubated): Obtain if inpatient + severe CAP or resistance risk. Adequate sample if >25 PMN and <10 SEC/lpf. NOTE: "abundant squamous cells" or more squamous cells than polys suggests the sample is saliva
  - **Blood cultures**: controversial benefit, positive <10-20% of inpt PNA
    - Obtain Scx and Bcx if: severe CAP, empiric treatment for MRSA/PsA, prev. MRSA/PsA, or hosp. w/ IV abx ≤90d
  - **Procalcitonin (PCT)**: ↑ in acute resp. infxn from bacterial causes. No validated threshold to distinguish bacterial vs. viral infxn. (ATS 2019;200:45). Can help in deciding to dc abx; dc if <0.25 or >80% drop from peak. (JAMA 2009;302:1059)
  - **Legionella urine Ag** (Sn 70%, Sp 99%); detects only serogroup 1 (80-90% in US). Check if severe CAP or recent exposure/travel. Clinical predictors include hypoNa, fever, diarrhea, and recent travel (CID 2019;68:2026)
  - **MRSA nasal swab**: high NPV (~98%). ⊖ test → consider d/c MRSA coverage (CID 2018;67:1)
  - **Influenza**: test seasonally. **Tx**: oseltamivir *(see URI page for tx indications)*
- **IDSA/ATS CAP Empiric Treatment** (NOTE: additional considerations for travelers, immunocompromised) (ATS 2019; 200:45)

Outpatient	Preferred	Alternative/Other info
No Comorbidities or MRSA/PsA RFs	Amox 1g TID OR doxy 100mg BID OR macrolide (azithro OR clarithro) (**if local resistance <25%**)	**NOTE: U.S. has high rates of macrolide- and doxy-resistant S. pneumo**
Comorbidities°	[Amox-clav BID *AND* azithro*] OR levofloxacin 750mg QD monotherapy	Cefpodox or cefurox. can replace amox-clav; doxy can replace azithro
Inpatient	**Preferred**	**Alternative/Other info**
Non-Severe	(β-lactam [CTX] *AND* macrolide [azithro]) *OR* levofloxacin monotherapy	Amp/sulb can replace CTX; doxy can replace azithro if macrolide or fluoroquinolone not tolerated
Severe/ICU	β-lactam (CTX 1-2g QD) *AND* (azithro OR levofloxacin)	**In ICU, azithro >> levofloxacin (anti-inflamm. effect)**; consider addt'l agents for drug-resistance (see below)
MRSA/PsA RFs	Vancomycin *AND* cefepime	Obtain Cx and nasal MRSA swab to inform de-escalation. Do not use daptomycin (poor lung penetration)
°Chronic heart, lung, liver, or renal disease; DM; AUD; malignancy; or asplenia.		

- **Risk factors for drug-resistant pathogens in CAP**:
  - General: hospitalization & IV abx in past 90d; prior respiratory isolation of MRSA, PsA or other resistant organisms
  - PsA: GNR on gram stain, h/o PsA, bronchiectasis, COPD w/ freq exacerbations req abx/steroids. **Tx**: *(for normal renal function)* cefepime 2g q8h, ceftazidime 2g q8h, pip-tazo 4.5g q6h, mero/imipenem; double coverage usually not necessary
  - MRSA: GPC clusters on gram stain, recent flu-like illness, necrotizing/cavitation/empyema, ⊕ nasal swab, risk factors for colonization (ESRD, PWID, prior abx [esp. fluoroquinolones]). Tx: vancomycin or linezolid
- Anaerobic coverage: only if suspicion for empyema or lung abscess, (see HAP/VAP & Aspiration Pneumonia)
- Steroids: Recent RCT showed benefit in severe CAP (NEJM 2023;388:1931). Meta-analysis showed steroids may lower risk of MV, no sig. impact on mortality (Chest 2023;163:484). IDSA/ATS do not have no rec for steroids. **AVOID** steroids in INFLUENZA as might ↑ mortality (Cochrane Rev 2016)
- **Duration**: usually **5d; 7d** in suspected or proven MRSA or PsA CAP, assuming clinical stability (afebrile x48h + ≤1 sign of CAP instability: HR >100, RR >24, O2<90%, AMS, no PO intake). MRSA should be treated longer if not improving within 72h (e.g. 10-14d in critically ill, 2-6w with ID consult if c/b bacteremia or necrotizing PNA)
  - If have not achieved clinical stability, extend course & eval. for resist. pathogen, complication (empyema, abscess), alt. source
  - Convert IV → PO when clinically improving; **no need to observe x24h on PO**
- **Response to therapy**: tachycardia resolves by 2-3d; fever resolves by 2-4d; hypoxemia resolves by 3-6d.
  - CXR clears by 1mo in 50% (up to 12wks in elderly, lung disease); **do not** need repeat CXR if clinical improvement
  - If no response to therapy after 72h: consider chest CT (± BAL) to evaluate for empyema, abscess, fungal infxn.
- **Parapneumonic effusion**: exudative, develops adjacent to a pneumonia, 20-57% of PNA hospitalizations (CID 2007;45:1480). Appropriately sized effusions need diagnostic thora for evaluation esp if concern for infx + need for extension of abx course.
  - **Definitions:** Uncomplicated (~pH >7.2/glucose >60, ⊖ GS/Cx) → complicated (requires drainage, pH <7.2/glucose ↓, still ⊖GS/Cx) → empyema (requires drainage, frank pus, + GS/Cx).
  - **Management**: Uncomp. effusions ok for abx alone if <1/2 hemithorax & free flowing; consider therap. thora if symptoms. Chest tube after diag. thora if: empyema, loculation, >1/2 hemithorax, thickened parietal pleura, sepsis w/ suspected pleural source (Chest 2000;118:1158; Ann Thor Surg 2018;105:1589)
  - Duration of abx, utility of surgery, timing of repeat imaging: guided by severity and clinical/radiographic progression

Infectious Disease HAP/VAP & Aspiration Pneumonia

HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA (IDSA/ATS: CID 2016;63:e61)

Definitions:

Hospital-acquired pneumonia (HAP)	Pneumonia that develops ≥48h after admission
Ventilator-associated pneumonia (VAP)***	Pneumonia that develops ≥48h after endotracheal intubation
Dx criteria: new/progressive infiltrates on CXR + 2/3 of fever, leukocytosis, purulent tracheal secretions	

***Ddx also includes non-infectious ventilator-associated events (VAEs) such as atelectasis, ARDS, pulmonary edema, and pulmonary embolism (Ann Transl Med. 2018; 6: 425; Infect Control Hosp Epidemiol. 2017; 38:867)

Common microbiology: enteric GNRs (*Klebsiella*, *E. coli*), MRSA/MSSA, *PsA*, *Acinetobacter*
Workup: CXR, SpCx, BCx, MRSA swab; consider induced sputum, bronch with BAL
MDRO RFs: **IV abx use w/in 90 days** preceding onset (most important); high local prevalence (>10%) of MDR GNRs & MRSA; structural lung disease (CF, bronchiectasis); prior hx of MDRO infection
- MDR VAP RFs: septic shock/ICU, ARDS, onset ≥5d in hospital, or RRT preceding onset

Empiric Tx of HAP/VAP w/ MDRO risk: 1 anti-PsA (**β-lactam** pref.) AND 1 anti-MRSA agent (typically **vancomycin**)
- Consider double PsA coverage if: septic shock, rapid progression of PNA requiring mech. ventilation, hx of MDR PsA
- Pulmonary toilet (oral hygiene including daily tooth brushing, oral and subglottic suctioning, mucolytics, etc.) (JAMA 2024; 184:131)
- For patients on vent ≥72 hrs, 3 days of inhaled amikacin may decrease rate of VAP (NEJM 2024; 2052-202)

Antipseudomonal β-lactams	Antipseudomonal non-β-lactams	Anti-MRSA agents*
- Cefepime 2g IV q8h - Ceftazidime 2g IV q8h - Pip/Tazo 4.5g IV q6h - Meropenem 1g IV q8h - Aztreonam 2g IV q8h (only if severe PCN allergy: Ellucid)	- Levofloxacin 750mg IV qd (*PsA susceptibility only 70% at MGH) - Ciprofloxacin 400mg IV q8h - Tobramycin 5-7mg/kg IV x1, then dose by level - Polymyxin B (call ID)	- Vancomycin IV - Linezolid 600mg q12h
**Daptomycin cannot be used for MRSA coverage when lung suspected source* *Always adjust dosing for renal function. When in doubt, call Pharmacy!*		

- **Tailoring therapy**:
  - Improvement after 48h or pathogen ID'd: narrow abx and d/c MRSA+PsA coverage if possible. ⊖ MRSA swab w/ 96% NPV for MRSA infection, most evidence comes from swab on admission and not further into course (CID 2018;18:67; CID 2020;71:1142). VAP: ⊖ tracheal aspirate NPV 94%, consider d/c abx after 72h (IJID 2010;14:18)
  - No improvement after 48h: broaden to cover MDROs (if not already), consider other sites of infection/abscess, non-infectious causes of clinical syndrome
  - MGH Ellucid Policy: HAP/VAP De-escalation Algorithm
- **Duration**: **7d**. Consider serial procalcitonin → d/c abx when <0.25ng/mL (ERJ 2009;34:1364; Cochrane Rev 2011;10)

ASPIRATION PNEUMONIA (NEJM 2019;380:651)

- **Definition**: pneumonia secondary to excessive secretions, particulate matter, or fluid into airways. Micro-aspirations are common and the definition of aspiration pneumonia as a distinct clinical entity remains unclear. Aspiration PNA/pneumonitis are often result of larger volume/frank aspiration events
- **Predisposing factors**: AMS/dementia, esophageal dysmotility, post-bronchial obstruction, post extubation, gum disease/poor dentition, seizure, tube feeding
- **Microbiology**: most common organisms are **GNRs and standard CAP/HAP organisms** (AJRCCM 2003;167:1650). Role of anaerobes is likely overstated (Chest 1999;115:178)
- **Characteristics**: indolent, putrid sputum, pulmonary necrosis w/ cavitation/abscess/empyema
- **Workup**: CXR, SpCx (anaerobic respiratory culture not performed at MGH due to low utility)
- **Empiric treatment**: same as CAP/HAP empiric treatment (AJRCCM 2019;200:e45; JHM 2020;15:754)
  - **Anaerobic coverage**: only recommended in pts w/ **suspected lung abscess** or **empyema**. First line: ampicillin-sulbactam if not severely ill, pip-tazo if severely ill, amox-clav if outpatient; *alternative*: (CTX+MNZ) *OR* clindamycin. If failure to improve on normal therapy; consider imaging to assess for abscess/empyema; may need source control.
  - **Duration**: **7d** unless complicated by cavitation/abscess/empyema
- No clear clinical benefit for abx for ppx for aspiration unless pt symptomatic (CID 2018;67:513)

ASPIRATION PNEUMONITIS

- **Definition**: aspiration of chemical substances into the airways *without* bacterial infection
- **Clinical manifestations**: abrupt onset (2h)**,** low-grade fever**,** ↑WBC, hypoxemia, CXR consolidation (RML/RLL upright, RUL supine) → *often indistinguishable from pneumonia in the acute setting*
- **Treatment**: no mortality benefit in initiating antibiotics in a patient with aspiration pneumonitis, however since it is clinically difficult to distinguish from PNA in the acute setting generally initiate empiric abx and reassess q24h → d/c if culture data remains negative *AND* if signs/sx/consolidation resolve rapidly

Infectious Disease Viral Respiratory/Head & Neck Infections

VIRAL RESPIRATORY INFECTIONS (for COVID-19 [VPN/MGH wifi]; for bacterial pharyngitis see *HEENT Concerns*)

- **Epidemiology**
  - >200 viral pathogens may cause VRIs, most common include rhinovirus, influenza, coronavirus, parainfluenza
  - LRTI (bronchitis, bronchiolitis, PNA): coronavirus, influenza, RSV, parainfluenza, adenovirus (Lancet 2011;377:1264)
  - In immunocompromised hosts, consider reactivation of latent viruses (e.g. CMV) if not on antiviral ppx
- **Presentation**
  - Transmission: hand contact, small droplets that become airborne, large droplet, peak viral shedding at 2-3d of illness
  - Symptoms: nasal congestion, rhinorrhea, dry/sore throat, cough, fever, conjunctivitis, myalgias w/ sx peaking at 3-5d and lasting 10-14d (if significant systemic illness consider influenza, COVID-19 >> measles, Hantavirus)
  - Complications: bacterial PNA (occurs in 1/800 w/ initial improvement → worsening after ~7d, micro: S. pneumo, S. aureus), asthma/COPD exacerbation, secondary bacterial sinusitis (occurs 2/100), otitis media, ARDS
- **Diagnosis**
  - Clinical diagnosis that generally does not require microbiological testing except for influenza and COVID-19
  - Resp. viral panel: at MGH NP swab PCR for COVID-19, Flu A/B, RSV; can help avoid unnecessary abx; collect within 5d of sx onset. Consider extended resp viral panel for immunosupp or high clinical suspicion with negative limited viral panel
  - Influenza testing: (IDSA: CID 2019;68:895)
    - RT PCR most sensitive and specific; can differentiate A, B and subtypes
    - Rapid Ag test 62% Sn, 98% Sp (<15min); during season ⊖ test does not exclude, not sufficient to stop tx
- **General Viral URI Treatment**
  - Sx management with decongestants, nasal sprays, anti-inflammatory agents, humidified air. NO role for ppx abx
  - COVID-19 specific treatments: remdesivir (NEJM 2020;383:1813), nirmatrelvir-ritonavir (NEJM 2022;386:1397), etc. in select patients. If using nirmatrelvir-ritonavir, ensure to check drug-drug interactions before initiating therapy. See Handbook (VPN or MGH wifi) for most up to date guidance.
- **Influenza Treatment and Post-Exposure Prophylaxis**
  - Treatment: oseltamivir 75mg BID x5d (can extend in severely ill or immunocompromised)
    - Indications: hospitalized pts and outpts w/ severe or progressive dz regardless of illness duration, ↑risk (age >65, long-term care facility resident, pregnant, <2 wks post-partum, immunosuppressed, cirrhosis, DM, CHF/CAD, CKD, COPD, SCD, asthma, BMI >40, neuro dz) also regardless of illness duration
    - Consider: outpts with sx <48h or those with high-risk household members
  - Prophylaxis: oseltamivir 75mg qd x7d if ≤48h post-exposure (x14d ± additional 7d after last case if outbreak at long-term care facility); switch ppx → treatment dosing if sx develop (IDSA: CID 2019;68:895)

HEAD AND NECK INFECTIONS (Principles of Crit Care. Chow AW. 4th edition. McGraw-Hill, NY 2015)

- Epidemiology: often from odontogenic, otogenic, or sinogenic infection with contiguous spread
- Organisms: Streptococci, H flu, oral anaerobes. PsA in otogenic source. MRSA in sinogenic source and PWID
- Diagnostics: blood cultures, **CT Neck**, MRI (consider to evaluate for osteo), IR or ENT for tissue or abscess culture
- Empiric Treatment: varies based on likely source; odontogenic – amp-sulbactam or CTX+MNZ, otogenic - cefepime+MNZ, sinogenic - vancomycin+CTX+MNZ. **Involve ENT early** for drainage and airway monitoring
  - **Submandibular space** (Ludwig angina): sources- periodontal infection, peritonsillar abscess, parotitis; p/w mouth pain, "double tongue," drooling, dysphagia can rapidly progress to airway compromise; polymicrobial esp viridans strep
  - **Internal jugular septic thrombophlebitis** (Lemierre syndrome): pharyngitis and septic emboli (esp lungs). Most commonly *Fusobacterium necrophorum* or viridans strep. Treat with (pip-tazo OR CTX+MNZ) ± anticoagulation
  - **Deep neck space**: involving retropharyngeal, "danger," or paravertebral spaces. Presents with neck pain and systemic toxicity. Can progress to carotid sheath abscess, mediastinitis, vertebral osteo, paravertebral abscess

ORBITAL AND PRESEPTAL CELLULITIS (Surv Opthalmol 2018;63:505)

	Preseptal/Periorbital	Orbital
Definition	Infection of anterior eyelid (not orbit or ocular structures)	Infection of orbit contents (fat, ocular muscles) but not the globe
Pathogenesis	Local trauma	Rhinosinusitis, oral abscess, dacryocystitis, local trauma, direct inoculation, ophthalmic surgery
Organism	Staph aureus, Strep spp.	Staph aureus, Strep spp; in immunosuppressed pt, consider Mucor and Aspergillus
Symptoms	Eyelid pain, edema, erythema ± chemosis & fever	Preseptal sx + pain with eye movement, proptosis, ophthalmoplegia w/ diplopia, fever & chemosis common
Diagnosis	Clinical; CT orbit and sinus to r/o orbital cellulitis	Clinical + CT orbit & sinus, blood cx; LP if c/f CNS extension, MRI if c/f cavernous sinus thrombophlebitis
Empiric Treatment	Augmentin 875mg q12h ± Bactrim 1-2 DS q12h (for MRSA coverage)	Vancomycin + CTX; add MNZ if c/f CNS involvement or odontogenic/sinogenic spread, involve ophtho early
Complications	Rare: eyelid necrosis, amblyopia	Vision loss, orbital/subperiosteal abscess, CNS spread

Infectious Disease — Urinary Tract Infections

Asymptomatic Bacteriuria

Definition: bacteriuria (≥10^5 CFU/mL) w/o sx referable to a UTI, irrespective of pyuria

- **Treatment**: asymptomatic bacteriuria or pyuria should NOT be treated (*exceptions*: pregnant woman, s/p renal transplant in past 1mo (controversial), treatment prior to invasive urologic procedures) (IDSA: CID 2019;68:1611)

UTI

Clinical features: frequency, urgency, dysuria (premenopausal), incontinence, nocturia, suprapubic tenderness in otherwise healthy nonpregnant women. In men w/ UTI sx, consider a dx of prostatitis, evaluate the prostate w/ DRE.

↓

Complicated UTI? Acute UTI + any of: fever, chills/rigors/sx of systemic illness, CVA tenderness/flank pain, pelvic or perineal pain in men, pregnant, renal transplant

No ↓

Uncomplicated UTI (Cystitis) (JAMA 2014; 312:1677)

- **Diagnosis**: clinical; U/A can be used to confirm; pyuria (>10 WBC); nitrite and LE both ⊕ on dipstick → Sn 68-88%
  - Women: dysuria + ↑frequency w/o vaginal discharge/irritation → >90% likelihood of UTI. Outpatient, U/A unnecessary unless immunocompromised or RFs for complicated UTI
  - Absence of pyuria *strongly argues against* cystitis
  - Nitrite: ⊕ w/ Enterobacterales (convert nitrate → nitrite)
  - Outpatient, get UCx if: male, atypical sx, persist 48-72h after abx initiated, or recur w/in 3 mo of tx
- **Differential diagnosis**: vaginitis, urethritis, structural abnormality, PID, nephrolithiasis
- **Microbiology**: *E. coli*, *Klebs, Proteus, S. Saprophyticus*, ***Enterococcus rarely causes true infection***
- **Treatment**: **NFT** 100mg BID x5d OR **T/S DS** BID x3d OR **fosfomycin** 3g x1; alternatives: oral β-lactam (e.g. Augmentin 500mg BID, Cefpodoxime 200mg BID) x7d, single dose aminoglycoside if c/f MDRO (Antimicrob 2019;63:e02165; MGH Policy Ellucid)
  - Avoid NFT if CrCl <40
  - Avoid empiric T/S if resistance >20% (*E. Coli* resistance 27% at MGH)
  - Avoid T/S and NFT in 1st trimester and term for pregnancy

Yes ↓

Complicated UTI

- 30% w/ UTI **and** fever are bacteremic (usually older, flank / suprapubic pain, ↑CRP, ↓BP) (JAMA 2018;378:48)
- **Pyelonephritis is a complicated UTI** & may itself be complicated by perinephric or renal abscess
  - WBC casts on U/A are suggestive of pyelo
- **Microbiology**: same as uncomp. UTI plus *Serratia*, *Morganella*, *Providencia*, *Pseudomonas, Citrobacter.* Gram-positives rare. If *S. aureus,* think bacteremia. Increasingly resistant organisms (especially to FQ, TMP/SMX)
- **Dx**: UCx in all; imaging if ill, suspect obstruction, persistent sx
- **Treatment**:
  -Outpt: **CPO** 500mg BID OR **LVO** 750mg x5-7d OR **T/S DS** BID x7-10d. Can give 1x IV CTX prior to oral tx.
  -Inpt: **CTX** OR **CEFE** OR **P/T**; CBPN if c/f ESBL. Narrow to oral if improving. Duration for inpt: depends on clinical course & oral agent chosen (5-7d for FQ; 7-10d for T/S; 10-14d for β-lactam), consult ID and IR for associated abscesses
  - Avoid **NFT** & **fosfomycin** (poor for upper GU track)
  - Remove/replace coated urologic devices
  - Prostatitis: **FQN** preferred for better penetration (can also consider TMP-SMX); tx duration up to **6w**

Catheter-Associated UTI (CAUTI) (IDSA: CID 2010; 50:625)

- **Definition**: leading healthcare-assoc. infection; requires: (1) s/sx with no other identified source of infection; AND (2) UCx with one uropathogenic species >10^3 CFU/ml from single catheterized urine specimen (catheter in place >2d) *OR* midstream voided specimen from pt whose catheter was removed w/in previous 48h
  - In pts w/ neurogenic bladder and ↓ sensation, other signs of UTI include new onset incontinence, autonomic hyperreflexia, malaise, lethargy, bladder pain (Urology 2015;6:321)
- **Prevention**: restrict catheters to pts w/ appropriate indications; remove catheters ASAP; consider short-term straight cath
- **Dx**: do not screen asx patients; pyuria, turbidity, odor cannot differentiate asymptomatic bacteriuria from CAUTI
  - **Remove/Replace** catheter ASAP, obtain repeat UA/UCx from new catheter PRIOR to abx. Catheters may become coated with a biofilm that acts as a reservoir for microorganisms and can compromise the action of antibiotics and host defenses
  - Purple urine bag syndrome: occurs due to byproducts from bacterial enzymes in urine; benign and ≠ UTI
- **Micro**: same as complicated UTI, with addition of *Candida* (see below); can be polymicrobial
- **Treatment**: same abx as complicated UTI, use Cx to narrow. If recent catheterization/instrumentation, h/o MRSA in urine, add vanc, then narrow pending culture results. Duration: 7d if improving; 10-14d otherwise

Funguria (IDSA: CID 2016;62:e1)

- Asymptomatic colonization common; only treat if symptoms present OR neutropenic OR before urologic procedure
- Tx: **Fluc** 200-400mg (pyelo) PO qd x14d *OR* for resistant *C.glabrata or* krusei, **Amphotericin** 0.3-0.6 mg/kg qd x1-7d

Recurrent UTI

- Behavior Δs: 2-3L water intake daily, post-coital voiding, avoid spermicide use, wiping front to back for pt. w/ female anatomy
- Abx ppx (usually ↓dose T/S or NFT) may be used in some ♀ w/ recurrent simple cystitis (≥2 UTI/6mo) if behavior Δs ineffective. Either post-coital or continuous if no temporal relation to sexual activity (Cochrane Rev 2004).
- Other inventions include: Vaginal estrogen for post-menopausal women (Cochrane Rev 2008), possible benefit from D-mannose 2g daily, methenamine hippurate 1g BID (BMJ 2022, 68229), cranberry products (Cochrane Rev 2023), and *Lactobacillus* probiotics.
- Pts w/ recurrent admission for complicated UTI, review prior micro & consider resistant orgs. Consider ID +/- urology involvement. *Abx ppx is not indicated for recurrent complicated UTI with resistant organisms due to risk of ↑ resistance*

Katie Kaugars

CELLULITIS (IDSA: CID 2014;59:147; JAMA 2016;316:325)

- **Clinical features**: erythema, warmth, tenderness, edema, induration ± purulence; smooth, often poorly demarcated. May have lymphangitis, LAD, vesicles/bullae, fever (20-77%), leukocytosis (34-50%)
- **Risk Factors**: trauma, venous stasis, chronic edema (esp. lymphedema), immunosuppression (DM, HIV), obesity, PWID, neutropenia, inflammation (eczema, psoriasis, radiation therapy), prior surgery/biopsy, toe web abnormalities
- **Diagnosis**: **CLINICAL.** Can use ALT-70 score to avoid abx. Cannot use if prior abx. (data req to calc: location, age, WBC, HR) (J Am Acad Derm 2017;76:618; JAMA Derm 2018;154:529). Consider US to assess for presence of drainable abscess.
  - BCx & wound Cx *NOT* recommended (low yield, pos in <10%). Obtain if: systemic tox, extensive involvement, immunosuppression, surgical wounds, special exposures (bites, water), recurrent/persistent cellulitis, extremes of age. 20-30% skin bx return pathogen.
- **Differential diagnosis:** (if "bilateral cellulitis," strongly consider alternative diagnosis)
  - Non-infectious: *inflammatory* (contact derm, drug rxn, Sweet syndrome, gout, bursitis, EN, pyoderma gangrenosum, GVHD); *vascular* (stasis dermatitis, DVT, superficial thrombophlebitis, calciphylaxis), *neoplastic* (leukemia cutis, lymphoma)
    - *Unilateral*: contact derm, gout, drug rxn, vasculitis, insect bite, DVT, vaccine site rxn, erythema ab igne
    - *Bilateral:* stasis derm, lipodermatosclerosis (often heavily pigmented, thickened subq tissue), lymphedema
  - Infectious: abscess, erysipelas (well demarcated, superficial cellulitis involving upper dermis & superficial lymphatics), nec fasc, septic joint/bursa, osteomyelitis, herpes zoster, HSV, Orf virus, erythema migrans, toxic shock syndrome, mycotic aneurysm
    - If abscess present, ddx includes: folliculitis, cyst, hidradenitis suppurativa (often intertriginous skin), lymphangitis
- **Treatment**: based on **1) purulence** and **2) severity**. Elevate affected limb. Duration: 5d; up to 14d if delayed signs of improvement

Severity	Purulent (abscess or fluctuance)	Non-purulent°
	MRSA >> MSSA > Strep	Strep >> *S. aureus* > aerobic GNRs
Mild	I&D only	PO: cefadroxil, cephalexin, diclox. pen VK , amox-clav
Moderate: systemic signs of infxn OR abscess >2cm	I&D+Cx. Empiric: TMP-SMX *OR* doxy MSSA: diclox. *OR* cephalex. MRSA: TMP-SMX	IV*:* cefazolin, CTX, pen G Severe ß-lactam allergy: vanc, telavancin
Severe: systemic signs of infxn *AND* HoTN, immunocomp., rapid evolution, deeper infection, or failed PO tx	I&D+Cx. Empiric: vanc *OR* LZD *OR* dapto *OR* ceftaroline. MSSA: nafcillin *OR* cefazolin	Vanc+(pip-tazo *OR* cefepime+MNZ). Nec fasc or TSS: add clinda for toxin inhibition
°Non-purulent w/ **MRSA risk factors*** (prev. MRSA infx/colonization, hosp./surgery/abx in prev 8wks, PWID, penetrating trauma, hemodialysis, HIV, athletes, prisoners, military, LTC facility residents): add empiric PO/IV MRSA coverage (TMP-SMX or doxy) *MRSA incidence increasing and many patients with MRSA infection do not have any risk factors (Med. Clin 2021; 4:723-725)		

NB: **erythema may worsen initially**; should improve w/ 72h of abx. **Document daily photos & draw margin lines**.

  - **Additional coverage**: *anaerobes* (if necrosis, crepitus, certain diabetic infxns [see below], animal bite); *GNRs* (cirrhosis w/ severe infection, immunocompromise, certain diabetic infxns [as below]); *PsA* (neutropenic, trauma, burns, post-op)
  - **Specific associations**: gas gangrene → *C. perfringens;* dog/cat bite → *Capnocytophaga*, *Pasteurella*; animals NOS → *Erysipelothrix*; human bite/PWID → *Eikenella*; freshwater → *Aeromonas*; saltwater→ *Vibrio vulnificus* (esp. cirrhosis)
  - **Sporotrichoid spread ddx**: sporotrichosis, Nocardia, NTM (e.g. *M. marinum*), Bartonella, tularemia
  - **PWID**: **infxn sources (H_2O, syringe, cotton filter, skin flora)**, share safe injection practices/PrEP (resources: CDC 1; CDC 2)
- **Prevention:** Compression therapy: ↓recurrence of cellulitis (v conservative therapy (education) alone). Patients should be advised to wear compression stockings daily to shift fluid away from the lower leg (NEJM 2020;383:630)
  - PCN ppx effective for reducing recurrent cellulitis over 6 & 12 month periods, but not once ppx stopped (PATCH, NEJM 2013;368)

NECROTIZING SOFT TISSUE INFECTIONS (NEJM 2017;377:2253)

- **Micro**: *Type I*: polymicrobial (mixed aerobes/anaerobes); *Type II*: monomicrobial (usually GAS > *Strep*, *Staph*, *Vibrio*, *Aeromonas*), associated with TSS; *myonecrosis* (i.e., gas gangrene): caused by *C. perfringens*, p/w tissue gas, severe pain, toxin-mediated shock
- **Risk Factors**: immunosupp., DM (e.g. Fournier gangrene), cirrhosis, neutropenia, EtOH, trauma, skin/mucosal breach, PAD
- **Clinical manifestations**: pain out of proportion to exam, bullae, induration (risk of compartment syndrome), tissue anesthesia, rapid skin changes (purple-red → blue-grey), crepitus (suggestive of myonecrosis); systemic toxicity, ↑CK, lactate, Cr, WBC
- **Diagnosis**: early suspicion and involvement of a **surgeon for surgical exploration** and **ID** is critical
  - LRINEC score ≥6 high suspicion for nec fasc (uses CRP, WBC, Hgb, Na, Cr, glucose); 90% Sn, 95% Sp (CCM 2004;32:1535)
- **Treatment**: urgent surgical debridement + abx: vanc + (mero or cefepime/MNZ or pip-tazo) + clinda (*NB*: LZD also inhibits toxin production). Adjunctive clindamycin may improve outcomes (Lancet Infect Dis. 2021;21:697)

DIABETIC FOOT INFECTIONS (IWGDF/IDSA: CID 2023;ciad527)

- **Severity**: mild (≥2 items: swelling, induration, pain, warmth, purulence); moderate (no systemic signs, erythema ≥2cm from wound margin or deeper than skin involvement); severe (systemic symptoms present)
- **Initial evaluation**: cleanse, debride, probe, culture. Check pulses/sensation, ABIs (40% have PAD).
- **Diagnosis**: Tissue specimen for cx > superficial swab. Often polymicrobial w/ GPCs>GNRs, anaerobes. Consider Bcx + ESR/CRP Consult inpatient wound service for deep culture. If c/f **osteomyelitis** *(see osteo)*
- **Treatment**: definitive tx based on deep Cx obtained **PRIOR** to abx initiation.
  - Mild (rx 1-2wk): oral → target GPCs (cephalexin, cefadroxil, amox-clav, diclox, levoflox); TMP-SMX or doxy for MRSA
  - Moderate/severe (rx 2-4wk): IV → target GPCs, GNRs ± anaerobes: (CTX or FQ) + MNZ; or amp-sulb. MRSA coverage w/ vanc, LZD, or dapto if: severe infxn, prior MRSA infxn/colonization, other RFs (see above). PsA coverage w/ cefepime or pip/tazo if: severe infxn, immunocompromised, neutropenic, water exposure, burn/puncture, nosocomial.
  - If improving, may de-escalate IV to highly bioavailable PO regimen to complete course of 1-2wk, up to 4 if slow to improve/PAD

Infectious Disease — Osteomyelitis

Clinical Manifestations

- **Acute**: <2wk of sx & absence of necrotic bone or sequestrum. *Sx:* localized, dull pain & diminished function, evidence of inflammation (fever/chills/night sweats/erythema). Patients may be afebrile
- **Chronic**: previously failed tx, >3wk sx, presence of bony sequestrum, persistent drainage or sinus tract. *Sx:* pain (absent if neuropathy), erythema, swelling, poorly healing ulcers; *hallmark is necrotic bone.* Fever may be absent
- **Etiologies**: hematogenous seeding (usually monomicrobial) from bacteremia (↑risk if endocarditis or indwelling device) or contiguous spread (polymicrobial) via direct inoculation after surgery/trauma
  - Hip, vertebra, pelvis: often have fewer symptoms, can present as septic arthritis
  - Vertebral: point tenderness, unremitting, >50yo (except PWID), ± fever (NEJM 2010;362:1022; IDSA: CID 2015;61:e26)
  - Pelvic: a/w bacteremia, sacral pressure ulcers, trauma (esp. athletes), urogyn/pelvic surgery, femoral access site; many present subacutely, may have localized pain or poorly localized, may not have fever
  - Sternoclavicular: anterior chest wall swelling, pain, tenderness; may be mistaken for abscess or atypical cellulitis; can occur via hematogenous spread or post-CT surgery ± mediastinitis
  - Mandibular: usually contiguous spread of oral flora/odontogenic infection; often w/ anaerobes
  - Foot: toe osteomyelitis or osteo a/w ulcer common in DM (IWGDF/IDSA: CID 2023;ciad527); PAD also risk factor

Diagnostic Approach (JAMA 2008;299:806)

- **Exam**: probing to bone sufficient for dx in patients w/ DM for foot OM (83% Sp, 87% Sn) w/o need for further imaging (CID 2016;63:944)
- **Blood Cx**: often ⊕ with hematogenous infxn involving vertebra, clavicle, pelvis (**always obtain BCx x2 before starting antibiotics**)
- **Labs**: ESR/CRP (if high can use for monitoring response) ± leukocytosis
- **Imaging**:
  - **>2wk of sx**: obtain plain XR first. If XR non-diagnostic and concerning story, obtain advanced imaging (MRI)
  - **<2wk of sx, suspected vertebral OM or DM**: start w/ advanced imaging (MRI), contrast preferred for vertebral OM
  - MRI: study of choice for further assessment after plain films; Sn 90%, Sp 82%, high NPV in foot osteo (Arch Intern Med 2007;167:125); best in DM or if c/f vertebral osteo (CID 2015;61:e26)
  - CT: if MRI not available; can demonstrate periosteal reaction & cortical/medullary destruction
  - Radionuclide bone scan: very sens, but non-spec (false ⊕ if soft tissue inflamm.); option if hardware precludes MRI
- **Bone biopsy**: **gold standard diagnostic test**
  - If diabetic foot infection, c/s vascular surgery, otherwise c/s ortho. If they decline, consult IR. Open Bx preferred to percutaneous (CID 2009;48:888). If perc. Bx ⊖ and suspicion high, repeat vs. obtain open biopsy
  - Bone Cx may be ⊕ even on abx; need 2 specimens: GS/Cx (aerobic, anaerobic, mycobacterial, fungal) + histopath
  - If evidence of OM on imaging or ⊕ probe to bone, bone biopsy ⊕ up to 86% of cases (CID 2006;42:57). Biopsy not required if ⊕ blood Cx and clinical/radiographic findings of OM

Risk Factors	Likelihood Ratio
Ulcer area >2cm	7.2 (1.1-49)
Probe-to-bone	6.4 (3.6-11)
ESR >70mm/h	11 (1.6-79)
Abnormal XR	2.3 (1.6-3.3)
MRI c/w OM	3.8 (2.5-5.8)
Normal MRI	0.14 (0.08-0.26)

Treatment

- **Antibiotics** (tx based on culture data, see table)
  - **Delay empiric tx until biopsy** if pt HD stable, has no neurologic compromise or e/o epidural abscess
  - Common organisms: **MSSA/MRSA**, CoNS, Strep, Enterococci, aerobic GNRs > Brucella, mycobacteria, fungi
  - Can consider adding rifampin if Staph + hardware (for biofilm) (Antimicrob Agents Chemother 2019;63:e01746)
  - Duration: ~**6w**, PO may be adequate after sufficient response to IV but d/w ID (OVIVA, NEJM 2019;380:425). If PO, FQ+RIF most common (RIF monotherapy not rec'd due to low barrier to resistance). Longer durations needed if prosthetic joint infection (NEJM 2021;384:1991; NEJM 2023;388:251) and ID should be involved. Retained hardware may require suppressive abx
  - No residual infected bone (i.e. amputation): abx 2-5d → up to 10-14 if associated SSTI
  - Consider trending ESR/CRP; if elevated at end of abx, consider further w/u (*NB*: NO routine repeat MRI, findings take weeks to months to resolve)
- **Surgical debridement**: indicated if failure to respond to medical therapies, chronic OM, complications of pyogenic vertebral OM (e.g., early signs of cord compression, spinal instability, epidural abscess), or infected prosthesis

Empiric Tx	
Vancomycin + GNR coverage (typically CTX 2g q24h). Include PsA coverage (cefepime) for PWID	
Organism-Specific Tx	
MSSA	Nafcillin 2g IV q4h; cefazolin 2g IV q8h
MRSA or CoNS	Vanc; dapto; dalbavancin (OFID 2018;6:ofy331)
PCN-S Strep	Pen G 4 mill U IV q4h; amp 2g q6h; CTX 2g q24h; vanc
Enterococci	Pen G 4 mill U IV q4h; amp 2g q6h +/- CTX 2g q24h; vanc; dapto
GNR	CTX 2g q24h; cipro 750mg PO BID; levoflox 750mg PO/IV q24h; cefepime 2g q12h (q8h if PsA)

Infectious Disease Bloodstream Infections & Endocarditis

BLOODSTREAM INFECTIONS (BSI)

Evaluation (JAMA 2012;308:502)

1. Sources: lines, procedures, meningitis, endocarditis, osteomyelitis (OM), septic arthritis, PNA, UTI, SSTI, abscesses
2. When should I/should I not send blood cultures? (JHM 2017;12:510; JHM 2016;11:336)

Predictive signs/symptoms	Predictive clinical scenario	Other Considerations
Fever+chills (+LR 1.1-6.1); **rigors** (+LR 4.7, Amer J Med 2005;118:1417); SIRS (-LR 0.09), normal food intake (-LR 0.18)	High risk: septic shock (38-69% ⊕ BCx), meningitis (53%) Medium risk: pyelonephritis (19-25%) Low risk: cellulitis (2%), CAP (7%), other community-onset fever (13%)	Immunocompromised (neutropenia, HIV); hard-to-isolate source (OM, septic arthritis)

3. How should I send blood cultures?
   - PRIOR to abx, 2 sets minimum, ideally 3 peripheral venipunctures over 1h; draw from central line only if c/f catheter-related infxn (criteria: catheter CFUs 3x peripheral blood OR cath. growth 2h before peripheral) (IDSA: CID 2009;49:1)
   - Signs of contaminant: only 1 bottle growing, certain organisms (e.g. CoNS, GPRs), no systemic sx, time to positivity >3-5d
4. Further testing:
   - Staph aureus and Staph lugdunensis: very sticky and *never* contaminants. **Daily surveillance cultures** (not necessary for GNRs) (CID 2017;65:1776), **remove lines/hardware**, **TTE/TEE** to r/o endocarditis, consider back imaging for discitis/OM if having back pain or imaging for pain at other joints and arthrocentesis for swollen joints
   - Consider TTE for high grade Strep spp. No routine TTE for GNRs
   - Yeast: **TTE**, **ophthalmology c/s** to r/o fungal endophthalmitis, **remove lines**

Antimicrobial selection:

GS	Empiric abx	Other considerations
GPCs	Vanc+CTX	S. aureus: **ID c/s** ↓mortality. Adding β-lactam (cefazolin/nafcillin) *may* improve outcomes (CID 2013;57:1760) MSSA: β-lactam >>> vanc (CID 2015;61:361)
GPRs	Call ID	More likely true infection in immunocomp hosts, multiple bottles, hardware, or known GPR infection
GNRs	Cefe/ceftaz/Zosyn	If MDRO, see IDSA guidelines. Can de-escalate to orals (TMP-SMX/FQN x7d) (JAMA IM 2019:179:3; CID 2019;69:7).
Candida	Micafungin	**ID c/s** ↓mortality (Lancet ID 2019;19:1336); ALWAYS treat as true infection in blood

ENDOCARDITIS (AHA/IDSA: Circ 2015;132:1435; ESC: EHJ 2015;36:3075)

- Etiology: cutaneous (40%), oral (29%), GI (23%) – source often unknown
- Clinical manifestations: BSI s/sx; valvular complications → acute HF, AV block; septic emboli (CVA/CNS, pulm/PE, MI, kidneys, spleen, joints), immune-complex deposition (arthritis, GN)
- Exam: new murmur, arthritis, embolic phenom. (petechiae, splinter hemorr)
- Diagnosis: **Duke criteria** → 2 major OR 1 major + 3 minor OR 5 minor
  - **TTE** in all; **TEE** if: ⊖ TTE w/ high susp; PVE; intracardiac device; suspected complications (AHA/ACC: JACC 2014;63:e57)**; consult ID**
  - May be role for PET in PVE (less so in NVE) (CID 2020;70;583)
- Monitoring: **repeat BCx** q24h until sterile x48h **& serial ECGs** for: new AV block (prolonging PR most common); p mitrale; low QRS voltage
- Micro: **NV**: Strep, Staph, CoNS/Enterococc., HACEK; **PV (<12mo)**: CoNS, Staph, Enterococc./GNR/fungus; **PV (>12mo)**: similar to NVE (w/ more CoNS)
- Indications for surgical consult: **emergent**: new-onset HF (acute valvulopathy), annular/aortic abscess (new AV block on ECG); **other**: L-sided S. aureus/fungus/MDRO, persistent infxn after 5-7d abx, PVE w/ recurrent infxn, large vegetation (>10mm on L, >20mm on R), embolic phenomena despite abx (AATS: JTCS 2017;153:1241); **can c/s surgery for all PVE** (± streptococcal)
- AC/antiplatelet: ok to continue but no indication to initiate; if CVA/ICH, hold x2w
- IVDU-assoc IE: refer to MGH Drug Use Endocarditis Team (DUET, Epic phrase: .MGHDUET). Includes CT surgery, ID, ACT

Modified Duke Criteria for Infective Endocarditis
MAJOR CRITERIA
⊕ **BCx (likely org.* in 2 separate Cx, rare causal org. in 3 Cx) or ⊕*C. burnetii, Bartonella* spp, *T. whipplei* PCR; *C. burnetii, B. henselae, B. quintana* IgG titer 1:800**
Endocardial involvement on imaging (echo or cardiac CT): vegetation, abscess, dehiscence, or new regurgitation; **PET/CT w/ abnormal endocardial activity**
MINOR CRITERIA
RFs: valve dz, IVDU, prior IE, CIED, prosthetic, CHD
Temperature >38C or 100.4F
Vascular phenomena: septic arterial/pulm emboli, mycotic aneurysm, ICH, conjunctival hemorrhages, Janeway lesions, cerebral/splenic abscess
Immunologic phenomena: GN, Osler, Roth spots, ⊕RF
Micro (not meeting major criteria, likely org*): ⊕ BCx, ⊕PCR from non-cardiac sterile body site
Imaging: PET/CT w/ abnormal metabolic activity w/in 3 mo of prosthetic cardiac implant

***S. aureus, S. lugdenesis, all Strep spp (except S. pneumoniae, S. pyogenes), Granulicatella spp, Abiotrophia spp, Gemella spp, HACEK, community-acquired enterococci** in absence of 1° **focus**

- IV → PO may be non-inferior to IV in **carefully selected** L-sided IE pts (POET, NEJM 2019;380;415)
- Ppx: if prior IE, prosthetic valve, unrepaired cyanotic CHD, or w/in 6mo of CHD repair, give amox. 2g or clinda. 600mg x1 (if PCN allergy) w/in 30-60 min pre-dental procedure; not recommended for GI/GU procedures unless ongoing GI/GU infxn (Circ 2007;116:15)

Organism	Therapy	Notes
Streptococci (VGS [*mitis, mutans, etc.*]; *gallolyticus* [*a/w colon cancer*]; *Gemella* spp.; *Abiotrophia* [treat as ↑MIC])	- **PCN** OR **CTX** x4w (some infxns may have 2w options) - may add gent based on PCN MIC and severity of infection - PVE: generally requires gent	- **Dosing**: PCN varies; CTX 2g q24; amp 2g q4; gent 1mg/kg q8, peak 3-4, trough <1 - **Vanc inferior to beta-lactams**
Staphylococci (*aureus; lugdunensis* [virulent, treat like *SA*]; CoNS [often methicillin-resistant])	- MSSA: oxacillin (better for CNS penetration), nafcillin (some risk for nephrotoxicity), cefazolin (good for kidneys) x6w - MRSA: vanc OR dapto x6w - PVE: may add gent for first 2w and rifampin for 6w	- **Dosing**: ox and naf 2g q4; cefazolin 2g q8; dapto 8-12mg/kg q24; gent as above - **Vanc inferior to beta lactams for MSSA**
Enterococci (*faecalis*, *faecium*)	- **Amp** AND **CTX** x6w, may add gent or streptomycin - Vanc if amp-resistant. VRE: dapto + amp OR linezolid	- **Dosing**: as above - 4w amp+gent sufficient if NVE and <3mo sx; 6w if >3mo or PVE
Gram ⊖ (HACEKs mostly, PsA, other GNRs possible)	- HACEK: **CTX** OR **amp** OR **cipro** x4w (6w for PVE) - GNRs: β-lactam + (AG or FQ) x6w	- Rare etiology, minimal data to firmly direct treatment modalities
Fungi (*Candida*, *Aspergillus*)	- Candida: **ampho B** 3-5 mg/kg/d (± **flucytosine** 25mg/kg q6h) OR **Micafungin** 150mg q24. **C/s surgery** (CID 2016;62:4) - Aspergillus: **vori** (6mg/kg q12h x2 dose load then 4mg/kg q12h) or **ampho B** (CID 2016;63:4)	- RFs: TPN, lines, PPM/ICD, prosthesis, IVDU

Shannon Cleary

BACTERIAL MENINGITIS

Clinical Features

- History: 95% have ≥2 of: fever, neck stiffness, AMS, HA (NEJM 2004;351:1849). Lethargy, hypothermia may be common in elderly. Abd pain, peritonitis can be seen w/ VP shunts. Can also cause seizures, stroke (infectious vasculitis), hydrocephalus, CN deficits (esp TB and fungal) (Continuum 2021;27:836).
- Exam: most findings more Sp than Sn. Nuchal rigidity 30% Sn, 68% Sp. Kernig's 5% Sn, 95% Sp. Brudzinski's 5% Sn, 95% Sp (CID 2002;35:46). Jolt sign (worsening HA with horizontal rotation of the head) 64% Sn, 43% Sp (Am J EM 2013;31:1601). May be absent if >65 yo, immunocompromised, taking analgesics (Continuum 2021;27:836-854). Meningococcemia with petechial rash, palpable purpura

Diagnosis (CID 2004;39:1267)

- Blood cultures **STAT** – **BEFORE** antibiotics (positive in 70% patients); **DO NOT** delay antibiotics for LP or imaging
- Lumbar puncture **ASAP**
  - Head CT prior to LP *only* indicated if: immunocompromised, known CNS disease (mass lesion, CVA, focal infection), new seizure, papilledema, ↓level of consciousness, focal neurologic deficit (Clin Neuroradiol 2022;32:857)
  - Obtain opening pressure with simple column manometer (nml 200mm H_2O; mean 350mm H_2O in bacterial meningitis)
  - For a list of studies to send and CSF analysis/interpretation, see **Procedures: Fluid Analysis**
  - Repeat LP if: no clinical improvement after 48h of appropriate antibiotics, evidence of antimicrobial resistance of cultured organisms, or ongoing fevers > 8 days w/treatment

Microbiology (NEJM 2011;364:2016; NEJM 2010;362:146; Cochrane 2015;9:CD004405)

Community			Nosocomial (intracranial procedure, >48h in hospital, head trauma)
Adults 18-34	Adults 35-49	Adults >50	
S. pneumoniae (50%) N. meningitidis (35%) H. influenzae (7%) GBS (6%) Listeria (2%)	S. pneumoniae (75%) N. meningitidis (10%) GBS (7%) H. influenzae (5%) Listeria (3%)	S. pneumoniae (76%) GBS (8%), Listeria (7%), H. influenzae (6%) N. meningitidis (5%) Aerobic gram neg bacilli	Gram neg bacilli (40%) S. aureus (10%) Coag neg Staph, particularly w/presence of foreign material (10%) C. acnes (takes 10 days to grow!)

Empiric Treatment (Lancet 2021;398:1171)

Adults < 50	Adults > 50	Immunocompromised	Nosocomial	SEVERE β-lactam allergy
Vanc + CTX 2g q12h	**Vanc + CTX 2g q12h + ampicillin** 2g q4h	**Vanc** + [**cefepime** 2g q8h OR meropenem 2g q8h] + **ampicillin** 2g q4h (not needed if on mero) (consider fungal & viral)	**Vanc** + [**cefepime** 2g q8h OR ceftazidime 2g q8h OR meropenem 2g q8h]	**Vanc + mero** 2g q8h OR moxi 400mg qd. [if >50 or immunocomp., for Listeria: Bactrim 5mg/kg IV qd div q6-12h] if not on mero

Note: vancomycin is added empirically to cover PCN-resistant S. pneumo, not MRSA

- Duration: N. meningitidis/H. flu (7d); S. pneumo (14d); Listeria (2-4w if immunocompetent; 4-8w if immunocompromised)
- **Dexamethasone**: greatest benefit in suspected/confirmed S. pneumococcal meningitis w/ GCS 8-11 (↓mortality/hearing loss, & short-term neuro sequelae in high-income countries) **0.15 mg/kg q6h x 4d**; start **prior to or with** 1st dose of abx, but **do not delay abx**
- CSF shunts: consult Neurosurgery for assistance with mgmt and/or shunt removal (IDSA: CID 2017;64:701)
- BBB penetration: meningeal inflammation ↑BBB permeability esp when severe. Abx with poor penetration into CSF in cases of mildly-inflamed meninges include β-lactams (overcome by ↑dosage), aminoglycosides, tetracyclines, daptomycin. See Tip Sheet.
- Prevention: MenACWY/MenB, Hib, pneumococcal vaccines. PPx: All close contacts of patients w/ **suspected** *N. meningitidis* or close contacts (w/ increased risk factors) of patients w/ Hib.

ASEPTIC MENINGITIS: meningeal inflammation with negative bacterial cultures

Clinical Features: similar to bacterial, usually less toxic. LP: **lymphocytic pleocytosis,** low CSF lactate (J Infect 2011; 62(4):255)
Etiology: *Infectious*: enteroviruses (most common), HSV2>1 (Neurology 2006;66:75-80), VZV, partially tx'd bacterial meningitis (usually days-wks), any stage of syphilis, Lyme, leptospira, mumps, Nocardia, TB, HIV (primary infxn), LCMV, fungal (see below), brain/parameningeal abscess; *Non-infectious*: autoimmune (Behcet's, sarcoid, SLE, SJS, Sjogren, GPA), neoplastic (leukemia, lymphoma), drugs (NSAIDs, antimicrobials, IVIG, immune checkpoint inhibitors), pituitary apoplexy
Additional diagnostics: West Nile IgM (June – Oct), VDRL, Lyme Ab, serum HIV, HSV swabs of any concurrent oral/genital lesions
Treatment: HSV, VZV → acyclovir 10-15 mg/kg IV q8h; tx underlying cause (if possible) & supportive care. **If suspect TB**, **c/s ID**

FUNGAL MENINGITIS: see *Invasive Fungal Infections*

Causes: *Primary (immunocompetent)*: Crypto, Blasto, Histo, Cocci, other dimorphic fungi; *Secondary (immunocompromised)*: Cryptococcus, Candida, Aspergillus, other molds; healthcare related outbreaks 2/2 epidural anesthesia in Mexico (CDC 2023)
Diagnosis: CSF CRAG, (1,3)-B-D-glucan, fungal wet prep, fungal culture, large volume (40-50mL) for Cx (J Clin Microbiol 2013;51:1285)
Treatment: ID to guide. *See* Invasive Fungal Infections.

ENCEPHALITIS (IDSA: CID 2008;47:303)

Presentation: abnormal brain function (vs. normal cerebral function in meningitis): AMS, focal neuro deficits
Etiology: *Infectious*: **HSV1>>2,** VZV, arbo (**West Nile**, WEE/EEE, St Louis, Japanese), enteroviruses (Coxsackie viruses, echoviruses, polioviruses), HIV, CMV (extremely rare), JC, adeno, influenza, Powassan virus, Zika; *Non-infectious*: post-infectious demyelination (ADEM), autoimmune, paraneoplastic (anti-Hu [SCLC], anti-Ma2 [testicular], anti-CRMP5 [SCLC/thymoma], anti-NMDA receptor [ovarian teratoma, idiopathic])
Diagnosis: send CSF for HSV, VZV PCR; other viruses less common. If clinical suspicion ↑ (West Nile IgM, JC, CMV/EBV [extremely rare]); autoimmune-Mayo ab panel; consider MRI (HSV→temporal lobe enhancement, W. Nile→basal ganglia/thalamic foci); EEG
Treatment: HSV, VZV → acyclovir 10 mg/kg IV q8h; otherwise supportive care (Neurol Clinic 2021;39:197). If sx recur s/p tx, consider viral relapse vs. autoimmune encephalitis – high rates of autoimm. dz wks later (Lancet Neurol 2018;17:760)

Infectious Disease C. Difficile Infection

OVERVIEW (IDSA 2021 update: CID 2021;73:1029; CID 2018;66:987)

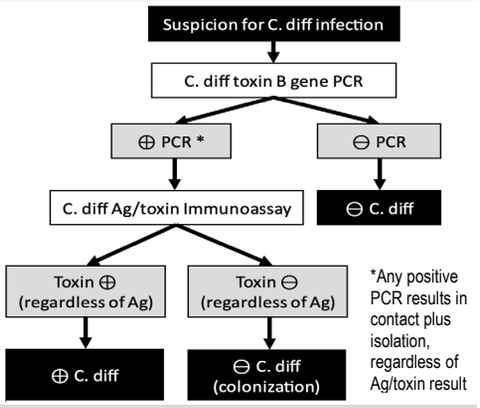
- Definition: C. difficile infection (CDI): acute-onset sx (usually ≥3 episodes/d of watery diarrhea) + e/o toxin-producing C. difficile or histopathology c/w pseudomembranous colitis
- RFs: **abx w/in 3mo** (particularly associated with penicillins, 2nd/3rd/4th gen ceph, FQ, carbapenems, clinda), ↑age (≥65yo), recent hosp or ↑LOS, severe comorbid illness, IBD, chemo/immunocompromise, GI surgery, tube feeding, PPI/H2RA
- Pathogenesis: fecal-oral via spores, colonized host; most often infection requires both acquisition of C. diff plus loss of gut microbial abundance/diversity (e.g. due to abx). Symptoms are toxin-mediated: toxin A (enterotoxic) & toxin B (cytotoxic)
- Community-acquired CDI: ~1/3 new cases; p/w diarrhea in pt w/o hospitalization in last 12 wks. *Potential sources*: contam. food/H_2O, pets, asx colonization in family, babies, outpt visits (AJG 2012;107:89; JAMA IM 2013;173:1359)

CLINICAL MANIFESTATIONS

- Features: **watery diarrhea** (≥3 loose stools in 24h) +/- mucus/occult blood; ileus, fever, abd pain, nausea,↑WBC
- Ddx: non-C. diff abx-associated diarrhea, infectious diarrhea, post-infectious IBS, IBD, microscopic colitis, Celiac disease
- Severity: see table below; severe colitis may be c/b hypovolemia, AKI, marked leukocytosis, lactic acidosis, protein-losing enteropathy; fulminant colitis characterized by hypotension/shock, ileus, toxic megacolon w/ ↑↑mortality

DIAGNOSIS

- **MGH protocol**: see algorithm to right.
  - Toxin B gene PCR: High Sn but can be ⊕ even in the absence of active infection (strain may have toxin gene but not produce it)
  - GDH Antigen: Enzyme produced constitutively by all C. diff strains; sensitive but cannot distinguish toxigenic & non-toxigenic strains
  - Toxin A/B: Assay detects toxin production, high Sp but poor Sn
- **DO NOT** retest within 7d w/o significant clinical change
- **DO NOT** test for "cure" (may remain ⊕ for up to 6w despite resolved sx)
- CT A/P: if severe illness or fulminant colitis to assess for complications warranting surgical intervention (e.g. toxic megacolon, bowel perf)
- Flex sig: in rare cases when alt dx suspected and need visualization/bx


Suspicion for C. diff infection
C. diff toxin B gene PCR
⊕ PCR *
⊖ PCR
C. diff Ag/toxin Immunoassay
⊖ C. diff
Toxin ⊕ (regardless of Ag)
Toxin ⊖ (regardless of Ag)
⊕ C. diff
⊖ C. diff (colonization)
*Any positive PCR results in contact plus isolation, regardless of Ag/toxin result

TREATMENT (IDSA 2021 update: CID 2021;73:1029; CID 2018;66:987)

Category	Criteria	Treatment
Non-severe	WBC <15 AND Cr <1.5	- **Fidaxomicin* 200mg PO BID x10d OR Vanc 125mg PO q6h x10d** - Alternative: metronidazole 500mg PO q8h 10-14d (if Fidax & Vanc not avail) - D/c antimotility agents, non-essential abx, cholestyramine (binds vanc)
Severe	WBC >15 OR Cr >1.5	- **Fidaxomicin* 200mg PO BID x10d OR Vanc 125mg PO q6h x10d**
Fulminant	Hypotension/shock, ileus, megacolon	**- Vanc 500mg PO q6h *AND* metronidazole 500mg IV q8h** - If ileus: can add **vanc PR** 500mg in 100cc NS as retention enema Q6H - **Surgery c/s**; consider FMT if ileus, tx nonresponsive, or recurrent dz
Duration: **10d** for non-fulminant; if receiving concurrent abx duration may be **extended** 7d after completion of other abx		

***Fidaxomicin**: 1st line, ↓ recurrence vs vanc; currently cost prohibitive at MGH (CID 2021;73:1029; Cochrane Rev 2017)

RECURRENCE

- Recurrent CDI: resolution of sx w/ tx, reappearance of sx w/in 2-8 wks after abx completed. Often due to relapse as opposed to reinfection vs. refractory disease (no resolution on therapy → consider alt diagnosis and ID or GI c/s)
- **1st recurrence**: Fidax* 200mg PO BID x10d OR 200mg PO BID x5d then qod x20d OR Pulse-tapered PO vanc 125mg x6-8w AND **IV Bezlotoxumab 10mg/kg x1 w/ fidax or vanc reg. if w/in 6 mos of prior episode** (CID 2021;73:1029)
  2nd recurrence: Fidax* regimen (same as 1st recurrence) OR pulse-tapered vanc 125mg x6-8w *OR* vanc 125mg q6 x10d followed by rifaximin 400mg TID x20d) AND **IV Bezlotoxumab as above**. IDSA recommends evaluation for **fecal microbiota transplant** (**FMT**) after 2nd recurrence; more effective than vanc or fidax alone (NEJM 2013;368:407; CID 2019;68:1351; Gastro 2019;156:1324). Consult ID for FMT evaluation.

OTHER CONSIDERATIONS

- **Infxn ctrl:** Contact precautions, wash hands with soap & water after contact (alcohol-based rubs won't eliminate spores)
- **Prophylaxis**: vanc 125mg PO qd for abx duration + additional 7d may ↓recurrence in pts w/ prior CDI receiving systemic abx (AJG 2016;111:1834; CID 2016;63:651; ICHE 2019;40:662). May also be effective as primary ppx in high-risk patients (≥60yo, current or recent <30d systemic abx) w/ 125mg daily dosing (CID 2020;71:1133)
- **Probiotics**: Not recommended for prevention of CDI by society guidelines (CID 2018;66:987). Some evidence supports use w/ abx to reduce abx-associated diarrhea (JAMA 2012;307:1959).

Infectious Disease

Invasive Fungal Infections

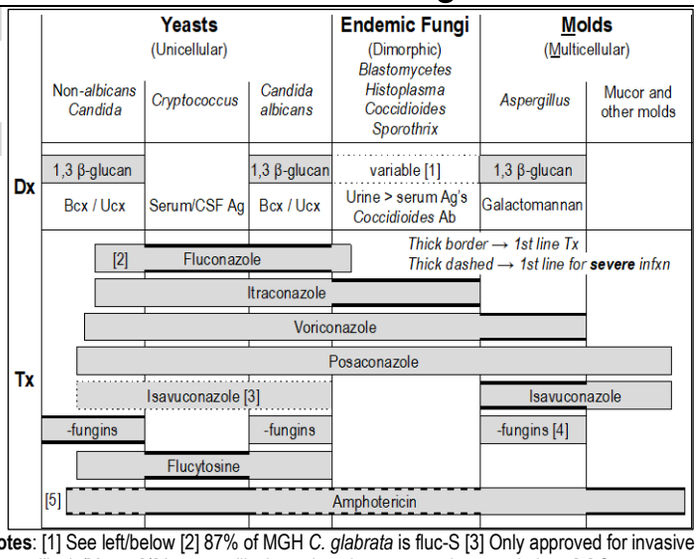
Risk Factors

Heme malignancy, **HSCT** > Solid organ transplant > biologic Tx, HIV/AIDS, prolonged neutropenia, prolonged glucocorticoids, burn patients, severe lung disease/prolonged intubation

Diagnostic Testing

Fungal markers:

- **1,3-β-D Glucan (BDG)** (CID 2011;52:750): cell wall polysaccharide, detects *Candida, Aspergillus,* PJP*, Fusarium, Trichosporon, Histo, Cocci* with Sn 77%, Sp 86% (cutoff 80). **CANNOT** dx Mucor, Rhizopus, Blasto, Crypto
  - **False** ⊕ w/ IVIG, albumin, HD, pip-tazo, unasyn, Strep, Pseudomonas (J Clin Microbio 2013;51:3478)
  - **False** ⊖ possible w/ candidemia (CID 2020;70:1925)
- **Galactomannan (GM)** (Cochrane Rev 2015): detects ***Aspergillus*** cell wall component; Sn (serum 65-80%, BAL 90-95%), Sp 88%
  - **False** ⊕ w/ some TPN formulations, IVIG, blood products
- **Histo Ag**: UAg Sn 90% if disseminated (vs. sAg 80%); Sp limited by cross-reactivity (esp. with blasto)
- **Crypto Ag (CrAg)**: serum Sn&Sp >90% if disseminated, ↓ w/ pulm dz only, ↑Sn for pulm if HIV
- **Blastomycoses**: uAg > sAg; ↑Sn, modest Sp d/t cross-reactivity. Sensitivity of uAg for pulmonary dz is ~80%.



Notes: [1] See left/below [2] 87% of MGH *C. glabrata* is fluc-S [3] Only approved for invasive Aspergillosis/Mucor [4] In aspergillosis, vori + mica not superior to vori alone [5] Covers most invasive fungi few exceptions, e.g., *C. lusitaniae, A. terreus, Lomentospora, Scedosporium.* Order amphoB w/ **pre hydration** *AND* **BMP, Mg** BID. *Adapted from JA Freed and AJ Hale, IDModules.com*

Invasive Opportunistic Fungi ****ID consultation is advised for these diagnoses**** *Aspergillus*, *Candida*, and *Pneumocystis* account for >80% of fungal infections diagnosed in hospitalized patients (OFID, 2022)		
YEAST	**Candida** CID 2016;62:e1	RFs: neutropenia, immunocompromised (heme malignancy, transplant, HIV/AIDS), TPN, PWID, CVC, prior abd. surgery, ICU Spectrum of illness: sepsis (25% mortality), macronodular skin lesions (10%), endophthalmitis, endocarditis, osteomyelitis, UTI Dx: **BCx** (**never contaminant,** grows slowly [BMC Infect Dis. 2013;13:486]), **c/s ophtho & ID, TTE**, repeat Cx daily. ↓Sn if deep tissue/hepatosplenic infxn; ⊕ RCx usually colonization not infxn. Ophtho c/s for dilated eye exam in non-neutropenic patients (if neutropenic, perform within first week of ANC recovery) (CID 2016;62:e1). Skin bx with cx if suspicious lesion. ***Candida score*** Tx: **BSI: echinocandins → azole** (amphoB for resistant strains); **remove CVCs**. **Endophthalmitis**: may need intravitreal amphoB/vori. **UTI**: see *UTI*. Duration: **BSI**: 2w after 1st ⊖ Cx w/ no dissemination, deep-seated infxn: longer, see *BSI*
YEAST	**Cryptococcus** Lancet ID 2024;9:s1473	RFs: immunocompromise (**HIV/AIDS**, malignancy, xplant), liver disease, **can** occur in immunocompetent (*C. gattii* > *C. neoformans*) Spectrum: asympt. → meningoencephalitis, (pulmonary [AHRF], skin nodules, liver abscesses); can be subacute, fever in ~50%. Dx: **serum/CSF CrAg (⊕ serum w/ ⊖ CSF = cryptoccal antigenemia)**, LP/CSF: OP >200 mmH2O, ↓gluc, ↑TP, lymphs, cryptococcomas on imaging, umbilicated skin lesions. Brain MRI and chest CT. Screen with serum CrAg if CD4<200 → LP if +. Tx: CM: **amphoB + flucytosine (x2w) → fluc (≥8w),** serial LPs if OP≥20 or symptoms of ↑ICP, **fluc** for mild pulm dz/antigenemia Ppx: fluc for HIV/AIDS (CD4<200) in high-risk, low-resource settings (in US not recommended unless positive serum antigen)
YEAST	**Pneumocystis** HIV.gov	RFs: immunocompromised (HIV/AIDS, heme malignancy, transplant), steroids equiv. to pred 20mg/day x4w Spectrum of illness: pulm sx onset over days/weeks, PTX, hypoxemia out of proportion to CXR (diffuse GGO on CT) Dx: **LDH >500** (Sn not Sp), **BAL > induced sputum** for silver stain/DFA **1,3-BDG** (Eur J Clin Micr ID 2014;33:1173) Tx: **T/S (PO/IV8-12mg/kg/d, adjust PRN renal fxn). Consider pred 40mg BID if severe hypoxemia**; Alternatives: TMP+dapsone, clinda + primaquine, atovaquone or pentamidine; Duration: 21d Ppx: T/S (1 DS qD > SS qD, 1 DS MWF), atovaquone, dapsone (check G6PD), pentamidine
MOLD	**Aspergillus** CID 2016;63:e1	RFs: neutropenia, steroids, transplant, COPD w/ prolonged ICU stay, anti-TNF, cannabis use, COVID19 with ARDS/ICU stay Spectrum of illness: invasive pulm (IPA), aspergilloma, sinus, tracheobronchitis, CNS, endophthalmitis, disseminated, necrotic skin Dx: **CT w/ halo sign**, **BAL**/sputum wet prep/fungal cx ± **biopsy**, serum **1,3-BDG** (not Sp), **GM** (Sp; trend serum in tx, BAL > serum) Tx: **voriconazole** (monitor trough, drug-drug int), Posaconazole or isavuconazole ; debride if necrotic. Duration: >6-12w for pulm dz Ppx: vori or **posa** (prolonged neutropenia, GVHD [NEJM 2007;356:348]), **vori/itra/inhaled amphoB** (lung transplant ± h/o IPA)
MOLD	**Mucor** Lancet 2019; 19:e405	RFs: DKA, iron overload, heme malignancy, prolonged neutropenia, immunocompromised (Semin Respir Crit Care Med 2015;36:692) Spectrum of illness: rhino/orbital/cerebral invasion, pulmonary, GI, renal; black eschars over ulcers, rapidly progressive Dx: **biopsy**, fungal wet prep/culture (broad **non-septate hyphae**), inform lab concerned for mucor, **CT w/ reverse halo sign** Tx: **DEBRIDEMENT**, **amphoB**, consider posaconazole or isavuconazole (for salvage therapy or if renal dz)
Endemic Mycoses* (maps)		
	Histoplasmosis CID 2007;45:807	Endemic areas: Central/eastern US (OH/MS River valleys), Central America, Asia, Africa Spectrum of illness: PNA, meningitis, mediastinal disease, disseminated disease, pericarditis, arthritis Dx: urine + serum Ag (improves sensitivity for detecting pulmonary infxn), histology, Cx. Chest imaging similar to sarcoid. Tx: **itra or fluc or no tx** (mild-mod), **amphoB → itra** (severe); NSAID for extrapulm; Duration: 6-12w Ppx: for both Histo and Blasto (below), consider itraconazole for HIV (CD4 <150) in hyperendemic areas
	Blastomycosis CID 2008;46:1801	Endemic areas: Midwest, south-central, SE US (OH/MS River valleys & Great Lakes), Canada Spectrum of illness: fever, PNA (acute or chronic), ARDS, ulcerated skin lesions, osteomyelitis, prostatitis, CNS Dx: wet prep (broad-based, budding yeast), Cx, uAg > sAg, **never a colonizer** Tx: **itra** (mild-mod), **amphoB → itra** (severe); Duration: 6-12mo
	Coccidiomycosis CID 2016;63:e112	Endemic areas: Desert regions: SW and S US, Mexico, Central & South America Spectrum of illness: PNA (+/- nodules), fever, rash (erythema nodosum), HA, eosinophilia, meningitis, osteomyelitis Dx: serologies, Cx (if high concern, alert lab for biohazard), spherules on bx/aspirate, Ag for extrapulm (urine, blood, CSF) Tx: **no tx** (mild-mod, immunocompetent); **fluc** or **itra**, consider **amphoB** (severe); Duration: 3-12mo Ppx: fluc for 1° ppx for transplant in endemic areas; fluc ppx for HIV in endemic areas if CD4 <250, newly (+) serology w/o evidence of active disease; fluc for 2° ppx

**Other endemic mycoses include: Paracoccidioidomycosis, Sporotrichosis, Talaromycosis, Emergomycosis (PLoS Pathog. 2019;15:9), etc.*

Infectious Disease — Tuberculosis

Epidemiology and Risk Factors

- World: 1/4 infected; US: incidence 2.4/100,000, w/ ~4% HIV coinfection and ~1% MDR (CDC MMWR TB US 2022)
- Acquisition: travel hx (if high-prevalence area), homelessness, incarceration, PWID, healthcare work, racial/ethnic minority
- Reactivation: risk 5% first 2y, 5-10% lifetime, higher if ≥1 risk factor: HIV, immunosupp, CKD (esp. RRT), DM, transplant, TNFα inhibitor, silicosis, malnutrition, tobacco, EtOH (NEJM 2011;364:1441); untreated HIV has 7-10% **yearly** risk

Screening for Latent TB

Test based on likelihood of exposure & progression to active disease. **IGRA preferred** (TSPOT at MGH); **TST acceptable** (NB: use TST/IGRA interpreter if BCG vaccinated). Both IGRA and TST are 80-90% Sn and >95% Sp in immunocompetent, ↓Sn in immunocomprom. Neither rules in/out active TB, can be **discordant ~30%** of the time. If ⊕ test w/ no risk factors, repeat either IGRA or TST prior to tx. If ⊕ test in ↑risk pt, proceed to tx (ATS/CDC/IDSA: CID 2017;64:111)

TST at 48-72h	Patient Population
≥5mm	HIV, prior TB hx, CXR c/w prior TB, silicosis, immunosuppression
≥10mm	Diabetes, CKD, PWID
≥15mm	No risk factors
Size reflects skin *induration*, NOT erythema	

Clinical Manifestations

- Primary TB: fever, chest pain, cough, arthralgia. CXR can be normal, have focal infiltrate, or ⊕ hilar LAD
- Reactivation TB: fever, cough, hemoptysis, night sweats, wt loss; CXR often w/ posterior/apical involvement or cavitation (seen in 1/3 of pts, a/w ↑org. burden → ↑infectious, AFB⊕) (J Clin Microbiol 2007:45:4064); more common than primary TB
- Extrapulmonary TB: meningitis with basilar predominance, Pott disease, GU involvement, intestinal TB, pericarditis, scrofula

Diagnostics: Active Pulmonary/Extrapulmonary TB (ATS/CDC/IDSA: CID 2017;64:111; Lancet 2007;369:9578)

Site of Infection		Diagnostic Tests
Lung	Sputum	Expectorated or induced, AFB smear/Cx x3 ≥8h apart (with one AM sample), add NAAT/PCR (Xpert) to one of the specimens; smear may be ⊖ if low burden (~20% if HIV-, ~60% if HIV+)
	Bronch	AFB smear, NAAT/PCR (Xpert), and Cx; +/- transbronch bx, post-bronch induced sputum ↑yield
Ascites or pleural fluid		Adenosine deaminase (ADA) >39 units/L→ high Sn/Sp; free IFN-γ elevated→ high Sn/Sp; AFB smear, NAAT/PCR (Xpert), & Cx (poor sensitivity but diagnostic if positive)
Pericardial fluid		AFB, Cx, cell counts (typically exudative, ↑protein, lymphocytes), ADA. No evidence for free IFN-γ
CSF		At least 3 large volume (10-15cc) serial LPs if possible (↑yield). ↓glucose, ↑protein, lymphocyte predominance; ↑ADA useful adjunct. AFB smear, Cx, and NAAT/PCR (Xpert)
Wound/Tissue		AFB-positive staining and caseating granulomas on pathology
Urine		UA w/ "sterile" pyuria; send first AM void (large vol ~50cc) Cx x3d. Urine LAM not available at MGH
Blood		Can send mycobacterial cultures (isolators) for AFB

Patient Isolation: clinical decision based on likelihood of active pulmonary TB

- When: cough, dyspnea, or hemoptysis + ≥1 risk factor (HIV+, foreign born, PWID, homelessness, recent incarceration, prior TB/exposure). First obtain CXR; if CXR normal (and HIV- or CD4>200), TB less likely. If CXR abnormal/equivocal (or HIV+ and CD4<200), maintain isolation & obtain sputum x3 as above. Consider ID c/s
- Discontinue: if alternate dx ***OR*** AFB smear ⊖ x3 w/ very low suspicion ***OR*** on TB tx x2w + AFB smear ⊖ x3 + clinical improv

Approach to Treatment (ATS/CDC/IDSA: CID 2016;63:e147; NEJM 2015;373:2149)

- **Prior to starting treatment**:
  - Check baseline LFTs/Cr, visual acuity/color discrimination, screen for HIV, Hep A/B/C, DM, EtOH use, pregnancy
  - Before treating latent TB: rule out active TB (obtain relevant history and CXR. Sputum AFB if ↑clinical suspicion)
  - Before treating active TB: **c/s ID**, send TB for drug sensitivity testing
- **Treatment regimens**:
  - Active TB: isoniazid (INH) + rifampin (RIF) + pyrazinamide (PZA) + ethambutol (EMB) x2mo, followed by INH+RIF x4mo
    - In 2022, CDC added 4mo rifapentine-moxifloxacin based regimen as option for drug-susceptible pulm TB
    - Obtain monthly sputum AFB smear/cx until ⊖ x2 consecutive months to assess tx response
  - Latent TB: INH+rifapentine (RPT) qw x12 (3HP) ***OR*** RIF x4mo (4R) ***OR*** INH+RIF x3mo (3HR) ***OR*** INH+B6 x6-9mo (6H, 9H, less preferred) (CDC Tx Table; R and R 2020;69:1)
  - Quinolones: 1st line w/ MDR-TB, **avoid in bacterial PNA** if suspicious for active TB (↓dx yield & ↑risk of resistance)
- Drug-resistant TB: **suspect if previously treated**, treatment failure, from prevalent area (India, China, Russia, S. Africa), or known exposure. Treatment regimen depends on drug susceptibility profile; usually 12-24mo course. High mortality
  - ATS/CDC/ERS/IDSA 2019 Guidelines for Drug-resistant TB (Am J Respir Crit Care Med 2019;200:e93)
- HIV co-infection: discuss timing of ART initiation w/ ID due to risk for IRIS
- Extrapulmonary TB: highly variable presentation/therapy, duration depends on site of infection & response. For CNS TB: 12mo tx, glucocorticoids confer 25% short term reduction in mortality (Cochrane Rev 2016)
- Medication side effects: hepatotoxicity (INH, RIF, PZA), optic neuritis (EMB), peripheral neuropathy (INH → add pyridoxine [B6] with initiation of treatment), orange bodily fluids (RIF), numerous drug-drug interactions (especially RIF)
- RIF/RPT remain widely used despite 2020 FDA announcement of nitrosamine impurities as perceived risk TB > cancer risk

Christopher Radcliffe

Infectious Disease HIV/AIDS & Opportunistic Infections

Definition and Clinical Manifestations

- Acute HIV: mono-like syndrome w/ rash, LAD, fever, oral ulcers, pharyngitis, myalgias, diarrhea; **presents 3-6w after infection**
- AIDS: HIV w/ CD4 count <200 *or* AIDS-defining illness

HIV Screening and Diagnostics

- **Screen** all 15-65yrs **once,** every **pregnancy**, dx of **another STI**, **PWID** annually, commercial sex (**CS**), MSM **>1 partner** since last test, partners of all ↑risk pts. MA: **verbal** informed consent req. HCP **can** consent for incapacitated pt (e.g. ICU)
- **Preferred**: 4th gen HIV 1/2 Ab/p24 Ag assay: mean detection limit **18d** (STD 2017;44:739). If +, f/u w/ HIV 1/2 Ab differentiation assay
- HIV RNA PCR (viral load, VL): mean **12d**, high Sn/Sp but slow, expensive; used for: 1) concern for **acute HIV** (Ab/Ag testing are negative early in disease course); 2) confirmation of HIV diagnosis; 3) treatment efficacy in known HIV

Prophylaxis

- **PrEP (Pre-Exp)**: offer to any pt w/ ↑risk of acquiring HIV: **serodiscordant** couple, **STI** last 6mo, inconsistent condom use, **PWID**, ↑risk sex (JAMA 2019;321:2203). Transmission risk near zero if HIV+ partner has undetectable VL (JAMA 2016;316:171)
  - Prior to initiation: negative HIV test, screen for HBV/HCV, other STIs, Cr, pregnancy test
  - Daily* regimen: **TDF/FTC (Truvada) qd ↓risk** (40-75%, >95% w/ excellent adherence), **d/c** when risk is no longer present. **TAF/FTC (Descovy)** also FDA-approved (except for pts w/ receptive vaginal intercourse) → ↑cost, wt gain, ↓renal/bone issues
    - *Injectable form (cabotegravir extended-release) also recently FDA approved (q2month) (NEJM 2021;385:595)
  - Event-driven PrEP: Truvada "2-1-1": double dose 2-24h before sex, then 1 dose daily x 2d (not FDA-approved). If discrete exposure (e.g. vacation), start Truvada qd 1w prior and for 1mo after (MSM only) (Lancet HIV 2019;7:113)
  - Monitoring: HIV q3mo, Cr q3-6mo (stop Truvada if eGFR <60, consider Descovy eGFR 30-60), STIs q3mo, pregnancy q3mo
- **Non-Occupational Post-Exp:** pts ≤72h after ↑risk exposure to HIV; case-by-case decision if HIV status of source unknown; check HIV Ab/Ag, HBV, HCV, STIs. Tx: 1) **Biktarvy,** 2)**Truvada** *or* **Descovy + doluegravir, x28d**; if ≥1 nPEP in last year, consider PrEP

Basic Evaluation for Newly Diagnosed HIV ****ID consultation is advised****

- CD4 count w/ %, quantitative HIV RNA (VL), genotype/resistance, CBC/diff, BMP, UA, lipids, 3-site GC/CT, syphilis Ab, TST/IGRA if no prior TB hx, Hep A/B/C, MMR w/ vax PRN, VZV if nonimmune, hCG, cervical and/or anal Pap, ± HLA B*5701 (IDSA: CID 2020)
- **Initiate ART early** through referral at all CD4 levels to ↓mortality (NEJM 2015;373:795); exceptions: crypto meningitis & therapy for HIV/TB co-infection (NEJM 2014;370:2487). ART can often be initiated prior to genotype, even in ↑risk pts (AIDS 2018;32:17)
- Recheck VL after 2-4w, then q4-8w until suppression achieved → monitor VL q3-4mo

Treatment: choose based on individual pt factors, DDIs, resistance, HLA B*5701 (abacavir hypersens.) (JAMA 2023;329:63)

- ART naive: 2 NRTI (typically TAF/FTC or TDF/FTC) + 1 of another class (often integrase inhibitor e.g. dolutegravir or bictegravir)
- Pregnancy: if new dx, 1st line TDF/FTC or abacavir-lamivudine (ABC/3TC) + dolutegravir; if prev well treated, cont existing regimen

Hospital Management of People with HIV

- **Patient on ART**: determine regimen & adherence; typically **continue ARVs** (interruptions can ↑disease progression)
  - If ARVs must be held, hold **all** ARVs and **c/s ID**. Beware drug-drug interactions esp ritonavir boosted PIs (check DDI database)
  - ARVs historically a/w with lactic acidosis (AZT, ddI, d4T) rarely used nowadays. If pt. has elevated lactate look for other causes.
- **Patient not yet on ART**: prioritize OI tx, ppx, **c/s ID** re: early inpt vs outpt initiation of ART
- **IRIS**: worsening sx of underlying infxn (TB, CM, MAC, CMV, others) 1-3mo post-ART initiation, ↑risk if ↓CD4 count
  - Early ART initiation safe after OI dx (PLoS ONE 2009;4:e5575) (**except** in CNS TB or crypto meningitis, or TB pericarditis)

Opportunistic Infections Prophylaxis Summary Recommendations for HIV in the US (HIV.gov 2020: Full, Tables)

CD4	Opportunistic Infection	Prophylaxis	Criteria for D/C
All	Influenza, HAV, HBV, HPV, VZV, *S. pneumo* (most common OI), TB	Vax: Flu; HAV, HBV, HPV, PCV15 or 20, PPSV23 after 8w; no live vax w/ CD4<200; LTBI: see *Tuberculosis*	None
<200*	*Pneumocystis jirovecii* (or hx of thrush) *screen for cryptococcus with serum CrAg	TMP-SMX DS qd (preferred) or 1 SS qd *or* dapsone 100mg qd *or* atovaquone 1500mg qd	CD4 >200 x 3mo
<150	*Histo* (hyperendemic or exposure; not in MA)	Itraconazole 200mg PO qd	CD4 >150 x 6mo
<100	*Toxoplasma*	TMP-SMX DS qd *or* dapsone 50mg qd + pyrimethamine 50mg qw + leucovorin 25 qw	CD4 >200 x 3mo
<50	*Mycobacterium avium* complex (MAC)	Azithro 1200mg q1wk if not on ART	When ART initiated

Treatment of Specific OIs in Adults with HIV (*review renal dosing for reduced GFR)

Pathogen	Diagnosis	1st Line Treatment
*See **Invasive Fungal Infections** for diagnostics and therapeutics for PJP and Cryptococcus, **Tuberculosis** for TB*		
Herpes Simplex Virus (HSV)	Oral/genital: DFA, PCR, viral Cx CNS: LP + CSF PCR	Orolabial: acycl 400mg PO q8h/valacycl 1g PO q12h x5-10d; Genital: tx x5-14d; CNS: acycl 10mg/kg IV q8h x3w
Cytomegalovirus (CMV)	Retinitis: ophtho exam; Colitis/esophagitis: bx; PNA: bronch w/ cytopath; Neuro: CSF PCR, brain Bx, Blood: PCR	Ganciclr IV → valgan PO w/ improvement. Consider foscarnet for resistant dz
Toxoplasma gondii	CT/MRI: ring-enhancing; most pts IgG+ but not IgM+, brain Bx if tx fails (to r/o CNS lymphoma)	Pyrimeth 200mg x1; then by wt + sulfadiazine + leucovorin qd x6w
PML	MRI: non-enhancing lesions; LP: JCV PCR	Only disease-modifying tx is ART
Mucocutaneous candidiasis (esophageal/oral)	Clinical dx: white plaque removed w/ tongue depressor, +KOH; EGD + Bx	Oral: fluc 100mg PO x7-14d; Eso: fluc 100-400mg PO/IV or itra oral soln 200mg PO qd x14-21d
MAC	Cx (blood/sputum/bronch/marrow/tissue), AFB stain	(Clarithro 500mg BID > azithro 600mg qd) + ethambutol 15mg/kg qd

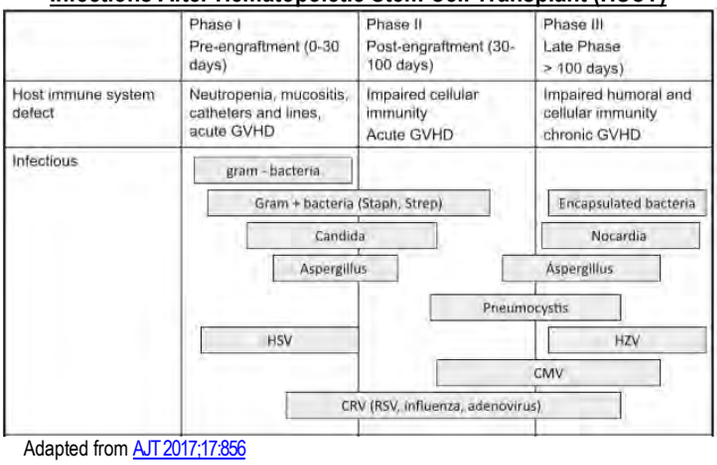
Infectious Disease

Transplant ID

General Principles (AJT 2017;17:856)

- **Early infections**: donor-derived, nosocomial/reactivation early, followed by OIs as immune suppression peaks
- **Late infections**: community-acquired infections, fungal infections
- **Pre-transplant evaluation**: check mumps/measles/rubella/VZV/CMV/EBV/HAV IgG, HBV (sAb, sAg, cAb), HCV, HIV, syphilis, Toxoplasma, TST/IGRA. Consider: endemic fungi (esp. Coccidioides), T. cruzi, Strongy. Goal: immunize or treat prior to txp
  - Serologic tests are helpful to identify latent infection pre-transplantation, but less useful after transplant for acute disease

Infections After Hematopoietic Stem Cell Transplant (HSCT)



Adapted from AJT 2017;17:856

Infections After Solid Organ Transplant (SOT)

	<4wk.	1-12mo.	>12mo.
Virus	Donor-derived	Adeno, BK	
		EBV, HCV, HBV	
		HSV	
		HHV 6,7	HPV, JC/PML, PTLD
		VZV	
		CMV, community-acquired	
Fungus		Aspergillus	Aspergillus
	Candida	Endemic fungi	Crypto
		Mucor	PCP	Mucor
Bact.	Surg.-related		Listeria, Nocardia	
			TB, non-TB mycobacteria
Para.		Toxo, leishmaniasis	
		Strongy, T. cruzi	

HSCT Prophylaxis (J NCCN 2016;14:882)

- **Candida**: fluconazole 400mg daily (d0-365 at MGH)
- **HSV/VZV**: famciclovir 250mg BID, acyclovir 400mg q8-12h or valacyclovir 500mg BID (d0-365)
- **PCP**: T/S (1 DS > SS qD, 1 DS MWF); also covers Toxo, Nocardia, Listeria; alternatives: atovaquone, dapsone (d0-180 or 365)
- **High-risk HBV reactivation**: entecavir or tenofovir
- **CMV**: pre-emptive monitoring of VL in high-risk pts & initiate tx (valganciclovir or ganciclovir) when ↑ in VL vs. **ppx** in high-risk pts. Letermovir (CMV-specific; no activity against HSV) can be considered for ppx in select cases (NEJM 2017;377:2433)

Select Transplant-Associated Infections *(ID c/s is advised)*

Pathogen	Clinical Syndrome	Diagnosis/Treatment	Additional comments
CMV	Fever, malaise, leukopenia, +/- hepatitis, colitis/esophagitis, pneumonitis	**Dx**: serum PCR (may be ⊖ in colitis, 15%) ± bx involved organ (GI, BAL w/ cytopath) **Tx**: PO valganciclovir vs. IV ganciclovir. Consider resistance testing if not improving (UL97, UL57). Alt Tx: foscarnet or maribavir (CID 2021;75:690)	Most common infxn s/p SOT. *Highest risk*: D+/R- in SOT and D-/R+ in HSCT. May ↑rejection and susceptibility to OIs. Repeat VL at least 7d apart ($t_{1/2}$ of CMV), not comparable between labs
PCP	Subacute dyspnea, hypoxemia, fever	See *Invasive Fungal Infections*	In contrast to HIV, there is limited data to support the use of steroids
BK Virus	Nephritis w/ AKI, ureteral stenosis, hemorrhagic cystitis	**Dx**: BK PCR +/- bx **Tx**: ↓immunosuppression	Mainly in renal txp (nephritis) and HSCT (hemorrhagic cystitis) pts
JC Virus	Progressive multifocal leukoencephalopathy (ataxia, hemiparesis, VF deficits, cognitive Δ)	**Dx:** MRI brain w contrast, LP w JC PCR **Tx**: ↓immunosupp, optimize ART	Mainly in pts with HIV, but also w heme malignancies, organ tx, and pts receiving lymphocyte-targeted agents
Strongyloides	*Hyperinfection syndrome*: fever, n/v/d, cough/wheeze, hemoptysis, ⊖ eos; 2° polymicrob. bacteremia (GNRs)	Ivermectin 200mcg/kg/d until stool ⊖ x2w	Identify at-risk individuals and tx pre-txp

Symptom-Driven Diagnostics

SOB	CXR, CT chest, induced sputum (GS/Cx, consider AFB stain, MB Cx, PCP exam), Legionella urine Ag (Sn 70-90%, Sp 100%), viral resp panel. **If cavitating or nodular lesions**: 1,3-β-D-glucan/galactomannan, sCrAg, urine/serum histo Ag, early bronch w/ BAL. *NB*: engraftment syndrome, cryptogenic organizing PNA also on DDx
Diarrhea	Stool Cx, O+P (consider micro add-on for: *Cryptosporidium, Cystoisopora, Cyclospora, Microsporidia*), C. diff, CMV PCR. If high suspicion for viral colitis (e.g., CMV, adeno), c/s GI re: colo w/ Bx. In HSCT, consider typhlitis (NEC) and GVHD
AMS/HA	CT head, LP (OP, GS/Cx, glucose, TP, HSV PCR, CrAg, save for more tests). *NB*: fludarabine, cytarabine, calcineurin inhibitors also a/w encephalopathy
Rash	Low threshold for skin biopsy (path + cx). GVHD, medication allergy, HSV, cellulitis, local vs disseminated fungal infection
Leukopenia	CMV PCR, EBV PCR, consider tickborne illnesses during the correct season or if frequent blood transfusions
Hepatitis	If post-HSCT, consider viral (HAV, HBV, HCV, EBV, CMV, HSV, adenovirus & more rarely enterovirus and HHV6), *Candida*, and non-infectious (GVHD, iron toxicity, DILI, hepatic sinusoidal obstruction syndrome)
AKI	UA/UCx, renal U/S, BK PCR if renal tx. Consider med toxicity and check levels (esp tacro, cyclosporine)

Infectious Disease STIs & Travel Medicine

SEXUALLY TRANSMITTED INFECTIONS; Routine STI testing in asymptomatic adults (CDC 2021)

	Lesions	Symptoms	Diagnosis	Treatment
Painless	Syphilis* (*T pallidum*) (CDC Pocket Guide; PCOI)	**1°**: painless, firm, round ulcer **2°**: fever, condyloma lata of skin/mucus membranes, rash, LAD, uveitis **3°**: aortitis/aneurysm, disseminated gummas, CN palsies, tabes dorsalis (impaired gait, sensation, reflexes) **Latent** = by definition, asx (early <1y; late >1y or unknown). Highly infectious in 1°, 2° *Neurosyphilis can occur at any stage*	**1st: anti-treponemal CMIA** (Sn & Sp >98%); generally, remains ⊕ for life **If CMIA⊕, lab reflexes to RPR.** RPR titer gives info on disease staging. Pregnany & anti-cardiolipin can cause false ⊕. CSF VDRL if c/f neurosyphilis (IJSTD AIDS 2006;17:768) **If CMIA ⊕, RPR⊖**: send out test to state for 2nd treponemal test (TPPA) to confirm CMIA⊕	**Prevention:** see DoxyPEP below** **1°/2°/early latent**: benzathine PCN G 2.4milliU IM x1 **3°/late latent**: benzathine PCN G 2.4milliU IM qw x3 **Neuro**: IV PCN G 3-4milliU q4h or infusion x10-14d (CDC 2021) **PCN allergy**: try to desensitize Serologic cure = RPR falls by factor ≥4
	LGV* (*C trachomatis* serovars *L1-3*)	**1°**: transient, painless anogenital lesion **2°**: 2-6w later, painful inguinal LAD **3°**: pelvic/abd LAD, inflamm diarrhea, abscess ("genitoanorectal syndrome")	Chlamydia NAAT detects LGV serovars LGV-specific PCR available as sendout test	Doxy 100mg BID x21d + aspiration of buboes (CDC 2021)
	GI/Donovanosis (*K granulomatis*)	Painless progressive beefy red ulcerative genital lesions	Presence of Donovan bodies in phagocytes on bx specimen	Azithro 1g qw/500mg qd x3w until healed (CDC 2021). Relapses can occur 6-18 mo s/p tx
Painful	Genital herpes (HSV2>1)	Prodrome → painful vesicles → ulcers 1° infection: systemic sx ± LAD	Confirm clinical dx with PCR of vesicular fluid from unroofed lesion	Acyclovir/valacyclovir. Consider episodic vs. chronic suppressive tx based on frequency, severity, & risk of spread (CDC 2021)
	Chancroid* (*H ducreyi*)	Painful genital/perianal ulcer 5-7d post-exposure w/ inguinal LAD ± drainage	Usually clinical with negative syphilis/HSV; GS/Cx, PCR in some labs	Azithro 1g or CTX 250mg IV (CDC 2021) x1; often empiric PCN for syph; eval partners

Discharge	Symptoms	Diagnosis	Treatment
Gonorrhea* (*N gonorrhoeae*), Chlamydia* (*C trachomatis*)	Vaginal/cervical: frequently asx, mucopurulent cervicitis, urethritis, PID Penile: dysuria, purulent discharge, epididymitis Pharyngitis or anorectal infxn possible	Vaginal/cervical: can self-swab, vaginal > urine NAAT (Sn >65%, >57%) Penile: first-catch urine NAAT > urethra Pharyngeal/anal swab based on hx (can self-swab) (BMJ Open 2019;9) *NB:* Cx if c/f resistance	Prevention: see DoxyPEP below** Gonorrhea: CTX 500mg IM x1, 1g if ≥ 150kg (CDC 2021); Chlamydia: doxy 100mg BID PO x7d > azithro 1g PO x1 (CDC 2021) Concurrent infxn/empiric tx for both: CTX + doxy (azithro-R gonorrhea) (MMWR 2020;69:1911). Eval partners†
Mycoplasma genitalium (Suspect in pts who fail tx for GC/CT)	Vaginal/cervical: cervicitis, PID, often asymptomatic Penile: dysuria, purulent discharge Anorectal: proctalgia, dyschezia	Vaginal/cervical: vaginal swab PCR Penile: urine or urethral swab PCR (send out test)	If failed tx GC/CT (e.g. with doxycycline): moxifloxacin 400mg qd x7-14d (esp. if macrolide-R) (CID 2015;60:1228)
Trichomoniasis (*T vaginalis*)	Vaginal/cervical: purulent malodorous discharge, pruritus, dysuria, dyspareunia Penile: usually asymptomatic	Wet mount → vaginal swab NAAT	Metronidazole or tinidazole 2g PO ±GC/CT tx; eval partner Retest after 3 months

Virus	Risk factors	Screening	Prevention
HIV*	Bacterial STI, inconsistent condom use, HIV+ partner, persons who inject drugs	See *HIV/AIDS & OI section*	PrEP *(see* HIV); condom use
HPV	Rectal HPV: receptive anal intercourse Cervical HPV: vaginal intercourse	Rectal: anal Pap, anoscopy Cervical: Pap per USPSTF	HPV vaccine series per USPSTF
Hepatitis B	MSM, PWID, >1 partner in 6 m, HBV+ partner, HCV, HIV, other STIs	HBs Ag (can have false + if recent HBV vaccine), HBs AB, HBc Ab	HBV vaccination series
Hepatitis C	MSM, HIV+, group / chem-sex, persons who inject drugs, intranasal cocaine, non-professional tattoo parlor	HCV Ab (remain + after tx), HCV VL if Ab+	Condom use, needle exchange, professional tattoos

*Reportable to public health department. Requirements for reporting other STIs may differ by state.
**DoxyPEP: Consider for trans women and MSM w/ + test for GC/CT or syphilis w/in 1yr. Doxycycline 200mg PO x1 within 72hrs of unprotected sex (oral, anal, or vaginal). Can reduce reinfection risk by >50% (NEJM 2023;388:1296). Not yet shown to be effective for other demographic groups (NEJM 2023;389:2331).
†In MA: After making a new chlamydia diagnosis, offer treatment for any partner w/i 60d without exam (instructions). Laws differ by state (CDC 2023).

TRAVEL MEDICINE

Pre-Travel Counseling

- Patient: medical conditions, med supply, dosing schedule changes for travel (e.g. insulin), supplemental O2 needs, allergies (epi pen), pregnancy, immunization history, prior malaria exposure
- Trip: duration, season, purpose of trip, exposures based on itinerary (urban v rural, cruise ship, animals, cave or water exposure)
- General Counseling: sunscreen (SPF 50+), seatbelt/helmet, safe sex, hand hygiene, animal avoidance, considerations re: tap water & raw foods, considerations re: travel & evacuation insurance, contingency planning if ill. Provide patient with CDC Travel Tips
- Arthropod bite avoidance: ↓exposed skin, insect repellant (DEET, picaridin, Metofluthrin, IR3535), treated clothing, mosquito nets

Immunizations: Ensure routine vaccinations are UTD, then use "Pre Travel PREP" or CDC site for country-specific recs; common travel vaccines: Influenza, Yellow Fever, Meningococcal, Typhoid, HAV, HBV, Japanese encephalitis, pre-exposure rabies, cholera
Malaria Prophylaxis (typically S/SE Asia, Africa, Central/S America): CDC tool: Rx options based on resistance. ~1w pre-travel, up to 4w after.
Daily: atovaquone-proguanil (Malarone), doxy, primaquine Weekly: mefloquine (a/w bad dreams; avoid if psych hx), chloroquine
Traveler's Diarrhea (CDC Yellow Book). Pathogens: ETEC, C. Jejuni, Shigella spp, Salmonella spp, Vibrio spp, norovirus, rotavirus, Giardia, etc.
Tx: *mild*: loperamide; *severe* (fever, dysentery, travel interference, age>70): azithro 500mg x3 > FQ or rifaximin, avoid loperamide
Infections in a Returning Traveler: Broad ddx, consider geography, exposure risk, pt vulnerability, incubation periods. Common culprits: Malaria, dengue, EBV/CMV, tick-borne, typhoid fever, respiratory viruses, TB, STIs, typical infections (CAP/UTI etc) (NEJM 2017;376:548)

TICKBORNE DISEASES (CDC Guide)

Approach to tick bites and prevention:
Physical prevention: daily tick check, shower after outdoors, check pets, clothing and gear, walk in center of trails (CDC handout)
Chemical prevention: DEET, picaridin, IR3535, lemon eucalyptus oil, para-menthane-diol, 2-undecanone; 0.5% permethrin for fabrics
Removal: ASAP, pull **straight out w/o twisting or jerking** w/ clean tweezers, then wash area w/ soap/water or rubbing alcohol
Approach to tickborne illness:
Hx: hiking/outdoor activity, late spring-early autumn. **Most (50-80%) will NOT recall tick bite** (Tick Borne Dis 2019;10;694)
Sx/signs/labs: fever, myalgias, arthralgias, rash; ↓WBC & PLT, ↑AST & ALT. **Coinfection is common**
Empiric tx: if high suspicion, send all dx incl. babesia smear (not tx by doxycycline), **start empiric doxycycline 100mg PO BID**
Other zoonoses to consider: tularemia (rabbits), leptospirosis (rats), brucella/coxiella (cows/sheep), though less common
Tick identity and geography (expanding iso climate change):
Amblyomma americanum (lone star/turkey tick, **Ehrlichia**): widely found in eastern US, more common in the south
Dermacentor variabilis (American dog/wood tick, **RMSF**): East of Rocky Mtns. (particularly southeast), limited areas of Pacific Coast
Ixodes scapularis (deer/bear/black-legged tick, **all others below**): **Northeast**, Mid-Atlantic, and central Midwest

Disease	Presentation	Diagnosis	Treatment
Lyme Disease (IDSA: CID 2021;72:e1; Lancet 2012;379:461; NEJM 2014;370:1724)	Early localized (days to 1 month): erythema migrans (3-30 d of bite, red ovoid lesion ± central clearing, 80% of pts), ± fever, fatigue, myalgia, arthralgia, HA, neck stiffness, regional LAD. Asx in 30% cases Early disseminated (wks-mos): multiple EM lesions, sx above ± migratory arthralgias 60%; neuro 15%: CN palsies, meningitis, mononeuritis, radiculopathy; cardiac 1%: heart block, myopericarditis; LAD; conjunctivitis, keratitis, retinal vasculitis Late disseminated (mos-yrs): **arthritis 60%** (mono- or polyarthritis of large joints, esp. knee), **neuro** (mild encephalopathy, peripheral neuropathy) Post-treatment syndrome (yrs): nonspecific sx; fatigue, MSK pain, cognitive dysfunction; NOT a "chronic infection" and no evidence of dysregulated immune response so no role for abx or IVIG (CRAI 2022:62:264)	**Avoid serologic testing w/o specific objective s/sx and endemic area/exposure** Early: can dx w/ clinical suspicion only (seronegative early on) Early & Late disseminated 1. Screening ELISA IgM/IgG 2. Western blot (WB) if screen ⊕ or **equivocal** IgM⊕ = 2 of 3 bands detected IgG⊕ = 5 of 10 bands detected IgG⊕ at 6-8w; if ELISA/WB IgM⊕ IgG⊖ at 6-8w: **false** ⊕	Early: doxy 100mg PO BID x10d OR Amox 500mg TID x14d OR Cefuroxime 500mg BID x14d Disseminated (neuro, cardiac involvement, arthritis): CTX 2g q24h x14-28d based on severity; check IDSA for specific recs on regimen Ppx: doxy 200mg PO x1 **IF** tick was attached & engorged ≥36h in endemic area *AND* ≤72h after tick removed
Babesiosis (IDSA: CID 2021;72:e49; NEJM 2012;366:2397)	Asymptomatic: 20% adults; no tx unless smear ⊕ > 1 mo. Mild-to-moderate: 1-4 wks after bite or 1-6 mos. from blood transfusion; **fever,** fatigue, chills, sweats, myalgias, anorexia, HA, n/v, cough – can be subacute (up to 6mo) Severe (usually immunosupp, malignancy, HIV, asplenic, >50yo): sx above w/ pronounced n/v, diarrhea, Complications: **severe hemolysis**, DIC, ARDS, multiorgan failure, CHF	Labs: DAT⊖ **hemolytic anemia**, ↓PLT, ↑ALT/AST Blood smear: ring forms in RBC (Maltese cross rare); parasitemia = %infected RBCs; monitor in immunosupp pts until neg smear PCR: very Sn & Sp, not widely available	Mild-mod: 7-10 d of atovaquone 750mg q12h + azithro 500mg x1 -> 250mg qd Severe: **c/s ID;** Azithro 500mg IV qd + atovaquone 750mg q12h; consider exchange transfusion if parasitemia > 10% or severe hemolysis or organ failure
Borrelia miyamotoi (Lancet Microbe 2022;10:e772)	**Relapsing fever**, HA, AMS, photophobia, chills, myalgias; ↓**WBC**/PLT, ↑ALT/AST (mimics anaplasmosis); rash usually absent; meningoencephalitis possible in immunocompromised (NEJM 2020;383:1578)	PCR > serology *NB*: EIA cross-reacts w/ Lyme	Mild: Doxy 100mg BID x14d Hospitalized: CTX 2g qd x 14-28d
Powassan virus (CID 2016;62:707)	Fever, chills, malaise, somnolence, n/v, **encephalopathy** MRI: T2/FLAIR hyperintensities (esp. basal ganglia) CSF: lymphocytic pleocytosis (can also be neutrophilic)	Serum/CSF serology (send-out to state lab): IgM ELISA, if + then neutralizing antibody testing	Supportive care, no antivirals known to be effective
Anaplasmosis **Ehrlichiosis**	Common: fever, malaise, myalgias, HA, n/v, arthralgias, cough; rash is less common (<30%) Labs: ↓**WBC**/PLT, ↑ALT/AST, ↑LDH, ↑ALP, ↑CK	PCR; morulae in neutrophils on smear in 20-80% of pts PCR; morulae in mononuclear on smear in 1-20% of pts	Doxy 100mg BID x 7-10d IDCNA 2015;29:341
Rocky Mountain Spotted Fever MMWR Recomm Rep. 2016;13:1	3-5d prodrome (fever, malaise, myalgias, HA, n/v) → progressive macular rash → petechial rash (limbs → trunk, spares face, end stage on palms and soles characteristic) Severe: meningoencephalitis, shock, ARDS, DIC, organ failure Labs: WBC variable, ↓PLT, ↓Na, AKI, ↑LFTs, ↑INR	Clinical dx: start empiric tx Serology: undetectable until 7-10d after sx onset; repeat 14-21d after sx onset to confirm PCR: special sendout Skin biopsy: 70-90% Sn	Doxy 100mg BID x5-7d minimum + ≥3d after afebrile (tx for all ages) Can consider load 200mg x1 if critically ill

Infectious Disease — Mpox & Ectoparasites

Virology and Epidemiology

Caused by **monkeypox virus**, an orthopoxvirus closely related to smallpox. **Three clades**: Clade I (Central Africa, ~10% mortality rate); Clade II (Western Africa, 0.1% mortality rate); Clade III (2022 global outbreak, related to clade II, low mortality). (NEJM 2022;387:1783).
Animal-to-human transmission: bites, infected animal fluids, preparation of bush meat. Rodents are likely reservoir.
Human-to-human transmission: direct contact with infectious lesions; respiratory secretions; transplacental; viral DNA found on fomites and bodily fluids (semen, feces, urine, saliva), but unknown if these are mechanisms of transmission
2022 global outbreak: 98% cases in MSM and close sexual contacts. 40% pts HIV+ (conflicting data on severity vs HIV- pts, likely more severe in uncontrolled HIV but confounded by delays in tx), 40% on HIV PrEP. Up to 30% associated with concomitant STIs. (HIV Med 2022;BMJ 2022;378:72410;Lancet 2022;400:661;MMWR Morb Mortal Wkly Rep 2022;71:1412).

Clinical Manifestations

Incubation period: mean 13 d, range 3-34 d
Prodromal phase: associated with viremia; 1-4 days with high fever, headache, fatigue, **lymphadenopathy**
Eruptive phase: 14-28 days with **mucocutaneous lesions** (including **palmoplantar**), progress from macules → papules/vesicles → pseudopustules (filled w/ debris rather than pus) → crusting and desquamation, may scar. Lesions **well circumscribed, umbilicated** a/w pain/pruritus. Clinical images: National STD Curriculum. 2022 outbreak commonly w/ **anogenital lesions** (NEJM 2022;387:679).
Complications:

- **Proctitis**: anorectal pain, bleeding, tenesmus, purulent discharge. Associated with receptive anal sex. Anoscopy not routinely performed due to severe pain. Risk of bowel obstruction, perforation.
- **Pharyngitis/tonsillitis**: pain may limit PO intake.
- **Ocular**: conjunctivitis, blepharitis, keratitis, blindness.
- **CNS disease**: demyelinating encephalitis/encephalomyelitis/transverse myelitis. LP consistent with viral meningitis but may be negative for mpox via PCR. (MMWR Morb Mortal Wkly Rep 2022;71:1212).
- **Superimposed cellulitis**: most common complication, in anogenital region may progress to Fournier's.

Diagnostics

Consider testing in patients with consistent rash and epidemiological risk factors → **c/s infection control/ID**; co-test for STIs, HIV.
Orthopoxvirus PCR: vigorously swab lesions to collect cells (do not attempt to unroof), collect 2 swabs/lesion and can swab multiple lesions. PCR of throat swabs and blood used for epidemiological, but not clinical testing.
Serologic testing: CDC IgM and IgG test → positive 5 and 8 days after rash onset
Lumbar puncture: if c/f encephalitis/myelitis → cell count, glucose, protein, orthopoxvirus PCR, IgM
Biopsy: may be helpful if multiple concomitant infections present (e.g. in immunocompromised patients). Lesions are positive for orthopoxvirus and histologically distinct from herpesvirus lesions.

Therapeutics

Most patients have mild disease, supportive care only. Hospitalization for complications and/or severe pain.
Tecovirimat (TPOXX): high preclinical efficacy but limited human data. Indicated for hospitalized pts, high risk pts (immunocompromised, pregnant, skin disease), or oropharyngeal/anogenital/ocular/CNS involvement. Most common side effects: fatigue, nausea, HA. Tx 14d. (JAMA 2022;328:134;Open Forum Infect Dis 2022;9:377;NEJM 2022;387:579;NEJM 2022).

- PO: take within 30 mins of fatty meal. 40-119 kg: 600 mg q12h; ≥120 kg: 600 mg q8h
- IV: contraindicated CrCl<30 mL/min. 35-119 kg: 200 mg q12h; ≥120 kg: 300 mg q12h

Cidofovir/brincidofovir: limited data suggests less efficacious than tecovirimat. Renal & hepatic toxicity. (Lancet Infect Dis 2022;22:1153).
Trifluridine/vidarabine eye drops: use w/ tecovirimat for ophthalmic infections, q4h 7-10 d, c/s optho. (Arch Ophthalmol 2003;121:715).
CNS involvement: c/s neurology, high dose corticosteroids for demyelinating encephalitis/myelitis (JAMA Neurol 2022;79:1180)

Prophylaxis

Vaccination: JYNNEOS → attenuated nonreplicating vaccinia virus, also confers smallpox immunity. Safe in immunocompromised patients. Involves two doses, the second dose given four weeks after the first. **Post-exposure prophylaxis:** Vaccination within 14 d of close/sexual contact with infected patient or presumed exposure (MSM who have had sex in areas where mpox is spreading). **Pre-exposure prophylaxis:** Offer vaccination for MSM/trans/nonbinary patients who have had at least one STI or >1 sex partners in last 6 mo, or any patient who has had sex at a commercial/public sex venue in last 6 mo. Limited data suggests breakthrough infections rare and mild (NEJM 2019;381:1897;NEJM 2022;387:2477).

Common Ectoparasites (Am Fam Physician 2019;99:635; NEJM 2020;382:2230)

- **Scabies**: Initial infxn w/o sx then intense pruritis ~6wk after inoculation 2/2 hypersensitivity rxn. Sx classically worsen at night. Exam w/ excoriated papulovesicles +/- burrows in interdigital spaces, intertriginous skin, wrist, inguinal region
  - **Rx:** 5% permethrin cream applied jawline downwards after bathing w/ removal after 8-14hr (reapply 7d later)
  - Clothing/bedding needs hot water (>130°F) + high heat drying **OR** 1wk isolation in sealed plastic bag
- **Lice**: Pruritis from saliva of lice. Live lice should be visualized. Nits ≠ infestation. W/o human blood meal, lice die ≤2d
  - **Rx:** head lice - 1% permethrin shampoo (re-apply 7-10d later since not ovicidal); pubic lice - 1% permethrin cream (reapply 9-10d later if persist + test for STIs + rx partners); body lice - laundry and hygiene +/- permethrin
  - Use high-heat (>130°F) laundering/drying exposed items + vacuuming **OR** 2wk isolation in sealed plastic bag
- **Bedbugs**: Suspect if recent travel. Crops of bites on exposed skin not covered by sheets or clothing. "Breakfast, lunch, and dinner" sign. Feces leave black debris on bedding + furniture. W/o blood meal, bedbugs can *still* live **70d**
  - **Rx:** Resistant to insecticides. Use mechanical methods. Clothing/bedding needs washed at high heat (>140°F). Can expose items to -4°F for 2hr. Physical removal via vacuum. Isolate items in plastic bags for prolonged periods

Infectious Disease

Fever of Unknown Origin

DEFINITION (NEJM 2022;386:463; CCM 2008;36:1330; Medicine 1961;60:1)

- Classically T>38.3C on multiple occasions for ≥3w, persisting w/o diagnosis despite ≥3d of inpatient investigation or 3 ambulatory visits (Curr Clin Top Infect Dis 1991;11:35; Br J Hosp Med 1996;56:21); newer recommendations call for T > 38 C (AMJMED 2022)

Special subpopulations: nosocomial (first fever > 24h of hospitalization), immunodeficient, neutropenic (current ANC<500 or expected in 1-2d), HIV-associated, travel-associated. **More often an atypical presentation of a more common disease than very rare disease.**

WORKUP (AJM 2015:128;1138e1)

- **Ddx**: In US, most commonly **rheumatologic** > **infectious** > **malignant** > **other**
  - 25-50% of cases, no source is identified (Medicine 2007;86:26)
- **History**: fever pattern, B symptoms, PMH (incl. dental hx, immunocompromise), valvular dz, exposures (travel, birthplace, animal, arthropod, food, blood products, sick contacts, sexual contact, drugs, occupation), TB risk factors, meds, vaccine hx, procedures/hospitalization, family hx
- **Exam**: dental caries/thrush, sinus and temporal artery tenderness, thyromegaly, murmur, abd tenderness, HSM, eyes, fundi, lymph nodes, joints, skin/nails, rectal, urogenital
- **Initial**: CBC, BMP, LFTs, ESR/CRP, UA/UCx, BCx x3 (diff. sites, min 5 d incubation),CXR, HIV
  - ESR: measure of chronic inflammation. Falsely elevated in ESRD, paraproteinemia, anemia, obesity, advanced age
    - **Correction for age → ♂: age/2, ♀: (age/2)+10**
  - CRP: rises more acutely than ESR; may be falsely low in cirrhosis
- **Other labs to consider**: IGRA, syphilis Ab, LDH, TFTs, SPEP/SFLC, ANA, ANCA, RF/CCP, cryo, CK/aldolase, EBV serologies, CMV PCR, ferritin, blood smear, HBV/HCV
- **Imaging** (Arch Intern Med 2003;163:545): CT C/A/P (71% Sn, 71% Sp), LENIs, TTE/TEE**, FDG-PET/CT** (Sn 86%, Sp 52%, 58% yield, vertex to toes and IV contrast recommended J Nucl Med 2016;57:1913, AJR 2023;221), tagged WBC scan (Sn 45-60%, Sp 78-86%), maxillofacial CT
- **Tissue diagnosis**: LN, liver (14-17% yield), BM (low yield at 0-2%), temporal artery (GCA), kidney (RPGN), LP if CNS findings

Etiologies of FUO	
*bold = common causes (OFID 2020;7:ofaa132)	
Infectious	Abscess (perianal, brain, dental), HIV, **EBV**, **CMV**, HHV6-8, HBV, HCV, **endocarditis** (fastidious/HACEK, nutritionally variant *Strep*), nosocomial infection, hardware/graft infection, **osteomyelitis**, septic arthritis, sinusitis, complicated UTIs, **TB (extrapulmonary),** tick-borne infections, endemic fungi (e.g. cocci/histo/paracocci), **malaria** (#1 cause in returned traveler, also now thought to be locally aquired in certain US states, CDC 2023), cat-scratch disease, toxoplasmosis, Q fever, brucellosis, bartonellosis, salmonella, typhus, melioidosis, schistosomiasis, visceral leishmaniasis, Whipple's disease, lymphogranuloma venereum
Malig.	**Lymphoma**, **leukemia**, MM, myeloproliferative disorders, **RCC**, HCC, CRC, **melanoma**, pancreatic, cervical, gastric, Castleman's
Rheum.	Cryo, **PMR**, **GCA**, RA, **Adult Still's**, **(JRA)**/MAS, **SLE**, dermato/polymyositis, sarcoid, HSP, PAN, Kikuchi's, Takayasu's, Behcet's, GPA/MPA/EGPA
Other	**Drug fever**, serotonin syndrome, NMS, **DVT/PE/hematoma**, hypothalamic dysfunction, pheo, **hyperthyroidism**, alcoholic hepatitis, **cirrhosis**, **IBD**, factitious, HLH, familial periodic fever syndromes (FMF, Hyper-IgD Syndrome, Schnitzler's, TRAPS)

TREATMENT

- **Try to avoid empiric antibiotics** and observe (unless hemodynamic instability or immunocompromised)
- D/C possible offending meds
- If ↑suspicion for GCA, strongly consider empiric steroids (prior to bx) to prevent vision loss/end-organ damage; must be reasonably convinced infxn/malig are excluded
- If extensive workup ⊖, prognosis usually good, most cases defervesce (AJM 2015:128;1138e1)

ETIOLOGIES BY PATIENT POPULATION

Patient Population	Etiologies
General (Am J Med Sci 2012;344:307)	Infection 14-59%, rheumatic 2-36%, malignancy 3-28%, miscellaneous 0-18%, undiagnosed 7-51%
Elderly patients (Am Geriatr Soc 1993;41:1187)	Infx 25% (abscess 4%), rheum 31% (most common GCA/PMR), malignancy 12%
Uncontrolled HIV* (CID 1999;28:341)	Infx 88% (dMAC 31%, PJP 13%, CMV 11%, histo 7%, other viral 7%), malignancy 8% (lymphoma 7%) *Mean CD4 count 58/mm^3; Immune reconstitution syndrome
Neutropenic (refractory to abx) (NEJM 2002;346:222)	Fungal infx 45%, bacterial infx 10-15% (resistant, biofilms), GVHD 10%, viral infx 5%, misc 25%
Returned traveler* (AJTMH 2013;88:397)	Falciparum malaria (77%), tyhpoid fever (12%), paratyphoid fever (6%), leptospirosis (2%), rickettsiosis (2%), dengue (1%)

*Only considers infectious etiologies, returned from Central or South America, Africa, Oceania, tropical and subtropical parts of Asia

SELECT CAUSES OF FUO

- **Drug fever**: dx of exclusion, broadly refers to any febrile response to medication. Can occur at any time while taking drug, with resolution post-cessation (resolution can take up to 1w)
  - Fevers can be in excess of >102F. Rarely, ⊕ accompanying signs (e.g., morbilliform rash, LFT elevations, eosinophilia)
  - Mechanisms include: hypersensitivity rxn (incl. SJS/TEN), dysfunctional thermoregulation, aseptic meningitis, Jarisch-Herxheimer reaction, NMS/serotonin syndrome, G6PD deficiency
  - Medications commonly associated: antimicrobials (β-lactams, sulfa, macrolides), AEDs, dexmedetomidine, chemo
- **VTE**: DVT, PE, thrombophlebitis may cause fever. Usually low grade (6% w/ fever >101F and 1.4% >102F) (Chest 2000;117:39)
- **Central fever**: most commonly associated with SAH, intraventricular bleed, brain tumors (JAMA Neurol 2013;70:1499)

Justine Enns

Infectious Disease

Rare Diseases at MGH

	Epi & Transmission	Symptoms	Labs	Diagnostic Tests	Treatment (c/s ID)
Malaria (*Plasmodium* spp)	Africa, Latin Am, Asia, Mid East, Eastern Europe *Anopheles* spp.	12-35d incub (up to yrs if *P. vivax*); fever, HSM, AMS, jaundice, petechiae	Anemia, ↓PLT, AKI, ↑LFTs, **↓glucose**, acidemia	**BinaxNOW** (RDT) + thick/thin blood smear w/ Giemsa	c/s ID; Variable *(see travel medicine)* Promising RTS,S vaccine
Mosquito-borne viruses: Dengue, Chikungunya, and Zika are often indistinguishable clinically/epidemiologically; consider testing for all 3 if concerned					
Dengue fever (DENV serotypes 1-4; *Flavivirus)*	India, Asia/Pac, Africa, Lat Am *A. aegypti* & *A. albopictus*	Fever, retro-orbital HA, arthralgia "**break bone fever"**, petechiae, shock	Lymphopenia, thrombocytopenia, **↑Hct**	<7d sx onset = NAAT; IgG/IgM (cross-rxn w/ Zika); tourniquet test	Rest, fluid; **avoid NSAIDs** due to ↑ hemorrhagic sx
Chikungunya fever (*Alphavirus*) **Zika virus** (*Flavivirus*)	Africa, Asia/Pac, **Caribbean**, Lat Am, S USA *A aegypti* & *A albopictus* (diurnal feeders); STI (Zika)	Fever (>102 in chik), HA, rash, polyarthralgia, conjunctivitis; Guillian-Barré syndrome + fetal microcephaly (Zika)	Chik: lymphopenia, thrombocytopenia, ↑LFTs, AKI Zika: labs freq. nml	Chik: PCR if <7d sxs; serology if ≥7d Zika: serology/plaque reduct.; serum/urine PCR if <7d of sx, serology if ≥7d of sx	Rest, fluid; avoid NSAIDs unless definitely not dengue. Chik: Rheum referral if pain >3 mo. Vaccine for Chik (IXCHIQ) if age 18+.
West Nile virus (*Flavivirus*)	Africa/MEast, Europe, Americas *Culex* spp. *(nocturnal)*	Asx; fever, HA, myalgia, 1% meningitis	CSF pleocytosis (lymphs)	**Serum + CSF Abs >** CSF PCR only for immunocomp. (c/s ID)	Rest, fluid
Leishmaniasis, cutaneous/visceral (*Leishmania* spp)	C/S America, S Europe, Mid East, E Africa, S Asia *Lutzomyia*/*Phlebotomus*	CL: painless ulcer(s), regional LAD VL: fever, HSM, ↓wt	VL: cytopenias, ↑LFTs	Clinical dx, skin bx PCR/smear/cx; rarely Ab	Variable, c/s ID; abx if superinfected lesions
Bacterial Zoonoses: *Coxiella*, *Bartonella quintana*, and *Brucella* are important causes of **culture-negative endocarditis**					
Cat scratch disease (*Bartonella henslae*)	Worldwide Cat bite/scratch, fleas	Fever, LAD 1-3w, neuro, ocular	↑ESR/CRP,↑LFT	Ab 1-2w; histology	Variable, c/s ID
Leptospirosis (*Leptospira* spp.)	Worldwide; tropics > temp. Water contaminated by animal urine/sewage	Fever, HA, myalgia, jaundice, conjuc. suffusion	**AKI, ALF, rhabdo**, anemia, hypoNa	Serology if 3-5d sx	Outpt: doxy 100mg BID x7d; inpt: PCN G, doxy, or CTX
Q fever (*Coxiella burnetii*)	Worldwide (except N.Z.) Aerosolized ungulate fluid	Fever, HA, myalgia, PNA, **endocarditis**	↑AST/ALT, ↑Bili, ↓PLT, ↑CK	Serology ≥7d	Doxy 100mg BID x14d
Brucellosis (*Brucella* spp)	Worldwide Dairy products, ungulate contact, lab exposure	Fever, arthritis (SI/spine), endocarditis	↑AST/ALT, ↓WBC w/ relative ↑lymph	Serology if 7-10d sx	Doxy 100mg BID x6w + gent/streptomycin or rifampin
Tularemia (*Francisella tularensis*)	N America, Europe > Asia Arthropod bite, animal contact (rabbit), food/water, airborne	**Regional LAD**; 6 syndromes: ulceroglandular, glandular, oculoglandular, pharyngeal, PNA, & typhoidal	Nonspecific; ↑ESR/CRP; ↓PLT	Serology if sx ≥2w; GS, Cx (cysteine + media)	Streptomycin or gent 7-10d; cipro or doxy 10-21d if mild dz
Rickettsia: in general, rickettsial diseases with eschars are scrub typhus, African tick-bite fever, RMSF, Mediterranean spotted fever, and rickettsialpox					
Murine typhus (*Rickettsia typhi*)	SE Asia, N Africa, N America Feces of infected rat fleas	Fever, **centrifugal rash**, HA, myalgia	↓Plt, ↑AST/ALT	Serology 2w apart	Doxy 100mg BID x7d
Scrub typhus (*Orientia tsutsugamushi*)	India → E Asia; Pacific, Chile Bites from infected mite larvae (AKA chiggers)	**Eschar**, fever, lymphadenopathy, centrifugal rash, HA	↓Plt, ↑AST/ALT, ↑Bili, AKI, WBC usually wnl	Serology 2w apart; consider eschar bx	Doxy 100mg BID x7d; azithromycin if tetracycline-R
Helminths: if concerned about intestinal worms, albendazole is an effective and safe medication to give empirically while awaiting lab results					
Schistosomiasis (*Schistosoma* spp)	Africa, Brazil, MidEast, Asia Fresh water with free cercariae from infected snails	Acute (3-8w): fever, urticaria, HA, swimmer's itch. Chronic: HSM, portal HTN, GN, hematuria, neuroschisto	**↑Eos** (30-60%) in acute, ↓Plt; LFTs usually wnl	Serology 6-12w; stool/urine microscopy for speciation	Acute: pred 20-40mg x5d + praziquantel Chronic: 40-60 x1 of praziquantel
Trichinellosis (*Trichinella* spp)	Worldwide, esp. Europe Undercooked meat, esp. pork	Abd pain, n/v, diarrhea → myalgia, weakness, ± fever	**↑Eos**, ↑WBC, ↑CK, ↑LDH	Serology 2-8d; muscle biopsy	Albendazole 400mg BID + pred 30-60mg qd x8-14d
Strongyloidiasis (*Strongyloides stercoralis*)	Rural tropics/subtropics; Appalachia, SE USA Skin contact w/ soil w/ human feces, fecal-oral, autoinfection	Skin rxn, epigastric pain, diarrhea, resp. sx; fever, n/v, sepsis/shock if hyperinfection	**↑Eos**, ↑WBC; hyperinfection & disseminated dz (in immunosupp.) w/ **normal eos**	Serology Sn > stool, but ↓ Sp. ✓ BCx, may have GN bacteremia (gut translocation)	Ivermectin 200 mcg/kg/day x2d; for 5-7d if disseminated. If from endemic region scr. for loiasis prior to tx. If RFs, scr. or tx prior to immunosuppression.
Other Infections					
Typhoid fever (*Salmonella enterica* serotype Typhi)	India, SE Asia, Africa Fecal oral; asymptomatic carriers	Fever, lethargy, abd pain, 'rose spots', diarrhea (>50%), constip. (30%), HSM	↓HR, ↑LFTs, ↓WBC (↑WBC sign of intest. perf.), anemia, abnl coags	Stool/blood Cx. BMBx 90% Sn. Serology effective in non-endemic regions	Azithro/ciprofloxacin Severe: CTX (meropenem if Pakistan or Iraq)
Melioidosis (*Burkholderia pseudomallei*)	SE Asia, Aus, US Gulf Coast Soil; aspiration, inhalation, percutaneous inoculation	Fever, PNA, skin abscess, community-acquired sepsis, GU	↑WBC; other nonspecific values c/w organ failure	Blood Cx on Ashdown's agar, GS	Abscess I&D + IV mero/ceftaz x2w → T/S x3mo
Hantaviruses	SW US, Lat Am, Eur., Asia Aerosolized rodent excreta	Hemorrhagic fever, renal failure, ARDS	↑PTT, ↓Plt, AKI, **proteinuria**	Serology via state department of health	Supportive care
Toxoplasmosis (*Toxoplasma gondii*)	Worldwide Cats; cont. meat/water	Mono-like symptoms	Atypical lymphs, ↑AST/ALT	Serology 1-7d; CSF 2-5d	Tx if CNS, chorioretinitis, or preg (consult MFM)

Multiple: NEJM 2017;376:548, NEJM 2018;379:557, NEJM 2007;357:1018, NEJM 2015;372:954, JAMA 2002;287:2391; Malaria: JAMA 2010;304:2048, J Clin Invest;2022:132, JAMA 2022;328:460; Dengue: NEJM 2012;366:1423; Zika: NEJM 2016;374:1552; Chikungunya: NEJM 2015;372:1231; West Nile: JAMA 2013;310:308; Cat scratch disease: Am Fam Physician, 2011;83; Brucellosis: NEJM 2005;352:2325; Schistosomiasis: NEJM 2002;346:1212; Typhoid: NEJM 2002;347:1770; Melioidosis: NEJM 2012;367:1035; Leishmaniasis: Am J Trop Med Hyg 2017;96:24; Coxiella: MMWR 2013;62.3:1; Strongyloides: Am J Trop Med Hyg 2017;97:645.

Infectious Disease — Infection Control

Resources: Infection Control websites on Sharepoint and Ellucid for the most up-to-date MGH policies and list of diseases/conditions requiring isolation. For additional support, work with unit-specific nursing leadership and contact Infection Control (x62036)

Standard Precautions: apply to *all* patients. **Hand hygiene (HH) is the most important action to stop the spread of infection. Please stay up-to-date re: source control for masking/hospital-approved eyewear.**

- Disinfect hands with an alcohol-based hand rub (ABHR)
  - Before entering and upon exiting the patient room
  - After contact with the patient or items in the patient environment
  - When glove use is indicated, HH is performed **before** donning AND **after** doffing gloves
  - Hands are visibly soiled: **wash** hands with soap/water, **dry** hands, then apply **ABHR**
- **Gloves/gowns** for **contact** w/ blood, bodily fluids (e.g., wound), secretions, excretions, mucous membranes, broken skin
- **Mask** + **eye** protection for procedures that can **splash** blood, bodily fluids, or secretions (e.g., ABGs, paracenteses)
- **Dispose** of materials **heavily soiled** with blood or bodily fluids into biohazardous waste (**red bag**)
- **Disinfect** reusable patient equipment (e.g., personal stethoscope, U/S) with hospital-approved disinfectant **wipes** according to instructions on label after patient contact/use

Transmission-Based Precautions (follow links in isolation column for additional details)

Isolation	Risk & Transmission	Description	Examples
Contact	Direct or indirect contact w/ pt or his/her environment	o Hand hygiene + nonsterile gloves + isolation gowns o **Do not touch** phones, beepers, notes while in room o Remove gown and gloves *together* only touching *inside* of PPE with bare hands, dispose of PPE inside or immediately outside the room o Dedicate the use of equipment (stethoscope, BP cuff) to avoid sharing w/ other pts. All equipment w/in the room is presumed contaminated o Disinfect reusable non-critical equipment (stethoscope) using hospital-approved disinfectant wipes for pathogen of concern	MRSA VRE MDROs CRE Disseminated HSV
Contact PLUS	Spore forming & alcohol-resistant orgs transmitted by indirect/direct contact	o Contact precautions + hand wash soap/water + ABHR + private room o After doffing PPE; wash hands with soap/water x15-20sec, dry, then apply ABHR; use bleach wipes for equipment o Isolate pt empirically while awaiting results	*C. diff* Norovirus *C. auris* Cutaneous anthrax
Enhanced	Cystic Fibrosis (bidirection protection)	o Contact precautions + private room and limitations on use of shared spaces	
Droplet	Large respiratory droplets (coughing, sneezing, talking)	o Surgical mask + eye protection + private room o Isolate pt empirically while awaiting results	*N. meningitidis* Influenza Rhinovirus Adenovirus Pertussis Mumps
Enhanced Respiratory	COVID-19	o Contact precautions + N95/PAPR + eye protection + private room (may cohort known with known COVID-19) o Airborne Infection Isolation Room (AIIR, "negative pressure") preferred when aerosol-generating procedures anticipated	COVID-19
Airborne	Small droplet nuclei that remain suspended in air & disperse widely	o Standard precautions + N95/PAPR + AIIR	Tuberculosis Varicella Disseminated VZV
Strict	Highly pathogenic organisms	o Contact precautions + N95/PAPR + eye protection + AIIR. If suspected, isolate, contact Biothreats (Non-COVID) Pager #26876	SARS/MERS Avian Influenza Variola (smallpox) Mpox

Immunocompromised Hosts:

- BMT, lung txp, neutropenic patients: standard precautions + positive pressure room + N95 for pt during travel + dietary precautions
  - BMT: gloves and surgical mask for healthcare workers
  - Lung transplant: gown, gloves, and surgical mask for healthcare workers
  - Note: Plants and flowers should not be allowed in immunocompromised host rooms due to risk of fungal infection

How Infection Statuses are Resolved and Transmission-Based Precautions Discontinued:
Use .Resolve (previously CORAL/NEMO) for all COVID-related infxn statuses. For screening for resolution of prior MRSA, VRE, MDRO status, please review MGH Resolution Policy and use .Resolve. Discuss resolving any other infection status w/ Infection Control

Bloodborne Pathogen Exposure: (needlestick, splash to eyes, mouth, nose, open cut), see *Exposures & Needle Sticks*

1. Immediately wash affected area
2. Normal business hours: call MGH OHS (6-2217). Outside business hours: page on-call OHS clinician, pager #21272. Can also page MGH needlestick consultant, pager #36222.
3. Notify supervisor. Floor charge nurse can help with paperwork and expediting any necessary patient labs

Pregnant Health Care Workers and Infectious Disease

Infectious Disease Antimicrobial Dosing

General guidance: if questions re: dosing should confirm with pharmacist. See MGH/Partners antimicrobial dosing guidelines

Drug (By Class)	Usual dosing	CrCl 50-25	CrCl 25-10	CrCl<10	HD
PENICILLINS					
Ampicillin IV (bacteremia)	2g q6h	CrCl 10-50: 2g q8-12h		CrCl <10: 2g q12h	2g q8-12h*
Ampicillin IV (endocarditis, meningitis, Listeria)	2g q4h	CrCl 10-50: 2g q6-8h		CrCl <10: 2g q12h	2g q8-12h*
Ampicillin-sulbactam IV (SSTI, intra-abd, PID)	3g q6h	CrCl 15-30: 3g q8-12h	CrCl <15: 3g q12h		3g q12h*
Piperacillin-tazobactam IV (non-Pseudomonas)	3.375g q6h	CrCl 20-40: 2.25g q6h		CrCl <20: 2.25g q8h	2.25g q8h
Piperacillin-tazobactam IV (Pseudomonas)	4.5g q6h	CrCl 20-40: 3.375g q6h	CrCl <20: 2.25g q6h		2.25g q8h
CEPHALOSPORINS					
Cefazolin IV	2g q8h	CrCl 10-50: 2g q12h		CrCl <10: 2g q24h	1g q24h* OR 2-3g post-HD
Ceftriaxone IV (bloodstream, bone, PNA, intra-abd, Lyme)	2g q24h	No change with renal function; meningitis/Enterococcal endocarditis dosing is 2g q12h to max 4g/day; on HD days, give post-HD			
Ceftriaxone IV (UTI, SSTI, PNA, intra-abd, SBP ppx)	1g q24h	No change with renal function; on HD days, give post-HD			
Ceftazidime IV (most indications; UTI can use lower doses)	2g q8h	CrCl 31-50: 2g q12h	CrCl 16-30: 2g q24h	CrCl 5-15: 2g x1→1g q24h; CrCl <5: 2g x1→1g q48h	2g x1 → 1g q24h* OR 2g post-HD
Cefepime IV (febrile neutropenia, PNA, CF, CNS)	2g q8h	CrCl 30-59: 2g q12h	CrCl 10-29: 2g q24h	CrCl <10: 1g q24h	1g q24h* OR 2g post-HD
Cefepime IV (others)	1-2g q8-12h	CrCl 30-59: 1-2g q12-24h	CrCl 10-29: 1g q24h	CrCl <10: 1g q24h	1g q24h* OR 2g post-HD
FLUOROQUINOLONES					
Ciprofloxacin IV (for systemic Pseudomonas, q8h dosing)	400mg q8-12h	CrCl <30: 400mg q24h			400mg q24h*
Levofloxacin IV/PO (CAP, complicated SSTI, MDR TB)	750mg q24h	CrCl 20-49: 750mg q48h	CrCl <20: 750mg x1 → 500mg q48h		750mg x1 → 500mg q48h*
CARBAPENEMS					
Meropenem IV (most except meningitis, CF, obesity in which case double dose)	1g q8h	CrCl 26-50: 1g q12h	CrCl 10-25: 500mg q12h	CrCl <10: 500mg q24h	500mg q24h*
OTHER ANTI-INFECTIVES					
Acyclovir IV (higher dose for CNS/VZV, adjusted wt if obese; recommend confirming dosing)	5-10mg/kg q8h	CrCl 26-49: 5-10mg/kg q12h	CrCl 10-25: 5-10mg/kg q24h	CrCl <10: 2.5-5mg/kg q24h	2.5-5mg/kg q24h*
Clindamycin IV	600-900mg q8h	Usual dose since clindamycin not renally eliminated; max 2,700mg/day			
Fluconazole IV/PO (invasive candidiasis, weight-based dosing if obese)	12mg/kg x1 → 6mg/kg q24h OR 800mg x1 → 400mg q24h	CrCl <50: 6mg/kg x1 → 3mg/kg q24h OR 400mg x1 → 200mg q24h			6mg/kg x1 → 3mg/kg q24h* *OR* 400-800mg x1 → 200mg q24h* (or 400mg post-HD)
Metronidazole IV/PO	500mg q12h	Most indications except CNS infection, C. difficile, H. pylori, & parasites			

***Dialysis dosing**: if drug dosed multiple times/day, administer 1 of the doses after HD. If drug dosed qd, administer after HD on HD days
Adapted from MGH/Partners antimicrobial dosing guidelines (contains more info on renal dosing for other antimicrobials, including **CVVH dosing**). To access, sign into VPN or Epic Resources→ Handbook → Entity Resources →Guidelines → Infectious Disease → Antimicrobial Renal Dosing Guideline (3a)

VANCOMYCIN DOSING including **HD/CVVH/PD dosing**:
Typical dosing regimen (if **stable** renal fxn): **20-25mg/kg** LOAD (can choose **higher dose** for **obesity** or **critical illness**, **max 2g** regardless of wt) → **10-15mg/kg q8-24h** (using adjusted body wt if obese) maintenance; adjustments for renal function (page 2 of empiric dosing guideline above). Dose by level for unstable renal function including AKI.

- **Monitoring**: Trough versus area under the curve (AUC) depending on indication - see table below. Check trough **1h prior to 4th dose** (or 3rd/5th to avoid overnight levels). AUC monitoring: PK calculation assistance from pharmacist, requires peak 1-2h after completion of (typically) 4th dose (usual infusion 60min/g) and trough 30-60min prior to next dose

SUMMARY OF THERAPEUTIC VANCOMYCIN GOALS	
Confirmed or high suspicion for serious MRSA infection (bacteremia, bone & joint, endocarditis/vascular, intra-abdominal, pneumonia, necrotizing infxns)	AUC_{24h} 400-600mg-h/L as determined by peak and trough, followed by patient-specific trough (pharmacist will place note in chart)
Serious non-MRSA infection or **empiric** use	Trough 10-20mcg/ml
Skin/soft tissue & **urinary tract infections**	Trough 10-15mcg/ml
Central nervous system	Trough 15-20mcg/ml
Unstable renal function (dose by level)	10-20mcg/ml

- **Subtherapeutic level**: first trough ≤1.5mcg from target (e.g. 9.3, w/ goal 10-15): continue same dose; first trough 1.5-5mcg lower than target (e.g. 11 w/ goal 13-18): ↑dose by 250mg (e.g. 1000mg→1250mg); first trough >5mcg lower than target: ↓dosing interval (e.g. q12→q8h) ± ↑dose
- **Supratherapeutic level**: ≤5mcg/mL higher than target: hold until level is expected to be within target and consider ↓dose; 5-10mcg/mL higher than target: hold until level is expected to be within target and consider ↑ dosing interval to next highest (8h → 12h); >10 mcg/mL higher than target: hold all future doses, reinitiate when random level ≤target range, ↑ dosing interval ± ↓dose

Hematology

Pancytopenia & Anemia

PANCYTOPENIA

Etiologies	
Infection	**Viral** (HIV, HBV/HCV, CMV/EBV, parvo), **bacterial** (brucella, TB), **fungal** (histo), **parasitic** (leish, malaria, schisto)
BM infiltration	**Malignant:** leukemia, MPN, MDS, MM, metastasis. **Non-malignant**: MF, infection, storage diseases
BM failure	**Nutrition**: ↓B12/folate/Cu/Zn, EtOH, anorexia. **Marrow suppression** from viral (HIV, hep, EBV, CMV, parvo). **Immune destruction/suppression**: AA, PNH, drugs, LGLL, SLE/RA, sepsis, HLH. **Ineffective hematopoiesis**: MDS
Destruction / sequestration	**Consumption**: autoimmune, DIC/TMA. **Splenomegaly**: portal HTN/cirrhosis, infection, autoimmune (SLE/RA), **others**
Congenital	Wiskott-Aldrich, Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, GATA2 deficiency, HLH
Work-up	
History	Time course, prior treatments/transfusions, autoimmune/onc hx, social, travel, occupational, infection hx; constitutional sx
Initial labs	**CBC/diff**, **retic**, **special slide**, **T&S**, LFT, TSH, Iron Studies, B12, folate, ESR/CRP, INR/PTT/fibrinogen **Also consider**: Cu, Zn, Vitamin E, LDH, haptoglobin, SPEP/SFLC, DAT, uric acid, ANA, HIV/HBV/HCV/CMV/EBV/Parvo, UDS
Review meds	NSAIDs, PPIs, sulfas, antihistamine, chemo, anticonvulsants, antiprotozoals, heavy metals, **many others**
Hematology	**Consult for**: unexplained significant neutropenia/thrombocytopenia, Blasts* on Diff, DIC/TMA, HLH, heme malignancy

Always consider the possibility of multiple independent cytopenias in addition to a unifying diagnosis

*Blasts first show up as 'Others' on a diff with a comment from the lab on their morphology until confirmed

ANEMIA (Williams Hematology 2021)

S/Sx: ↓O2 delivery → fatigue, lightheaded, DOE, pallor, angina (if CAD), claudication, cramps, abd pain, N/V; compensatory mechanisms → ↑RR, ↑CO (↑HR, palpitations, flow murmur, later: high-output HF), ↑erythropoiesis (bone pain)

Other findings: dark urine/jaundice (hemolysis), glossitis (folate/B12/Fe def), motor/sensory deficits (B12 def), pica/koilonychias/angular cheilitis/RLS (Fe def), splenomegaly (cirrhosis, infxn, thalassemia, malignancy, chronic hemolysis), constipation/bone pain (myeloma), melena (GIB), heavy menstrual bleeding, unusual thromboses (PNH), petechiae/purpura (coagulopathy, pancytopenia), family hx (thal/SS)

Initial labs (draw/add on **prior to transfusion**): **CBC/diff** (Δs in other cell lines, **MCV**, RDW), **retic**, **special slide, T&S**

- Calculate **reticulocyte index** **(RI)** = [% retic x (Hct/nl Hct)] / maturation factor, adjusts for Hct/early release of retics. Determines if adequate BM response: **hypo- (<2%) vs hyper-proliferative (>2%)**; **RI <0.1%** indicative of aplastic anemia or red cell aplasia

Additional labs depend on RI and clinical history:

- **RI <2% → "Anemia labs"**: Fe/TIBC/ferritin, folate/B12 (in last 6mo), BMP, LFTs, TSH, CRP, review prior CBC
  - If unrevealing/otherwise indicated by history: ± SPEP/SFLC, Hgb electrophoresis, AM testosterone, Epo, BMBx
- **RI >2% → "Hemolysis labs" vs recent bleeding**: LDH, bilirubin, haptoglobin, DAT (Coombs), coags, UA

CLASSIFICATION OF ANEMIA (NEJM 2014;371:1324; Lancet 2018;391:155; JACC: Heart Failure;2019;7:36; Williams Hematology 2021)

UNDERPRODUCTION (RI <2%)

Microcytic (MCV <80 μm³)	**Normocytic** (MCV 80-99 μm³)	**Macrocytic** (MCV ≥100 μm³)
Iron deficiency anemia (IDA) • ↓Fe, ↑TIBC, ↓ferritin (<30 high Sp; <15=⦸Fe in BM), Fe/TIBC <16%, <20% with inflammation, ↑RDW **Anemia of inflammation/chronic dz (ACI/ACD)** • ↓Fe, ↓/nl TIBC, ↑ferritin (<100 if ACI+IDA or <200 in ESRD), Fe/TIBC ↓/nl (>18%) • In CHF (concomitant IDA/ACI), ferritin <100 (or <300, if Tsat <20) **Thalassemias** • Fe studies nml, MCV ↓↓ (often <70), Mentzer index (MCV/RBC <13; high Sp); Hb electrophoresis **Sideroblastic anemia** • ↑ferritin, Fe/TIBC nml; smear: basophilic stippling (Pb); BMBx: ringed sideroblasts	**Inflammation & variant**: • Early IDA or early ACI • Mixed IDA & ↓folate/B12 (dimorphic: nml MCV w/ ↑RDW) **Organ-specific**: • **Renal** (CKD/ESRD): ↓Epo (should ↑10x per 10% Hct drop) • **Endocrine** (thyroid, pituitary, adrenal, parathyroid, testosterone; ↓metab rate→↓O2 demand) ->↓Epo secretion • **Marrow** (red cell aplasia, aplastic anemia, MDS, myelofibrosis, myelophthisis, PNH, MM): check SPEP, serum FLC, BMBx	**Megaloblastic**: *smear shows hyper-seg PMNs and macro-ovalocytes* • **↓Folate**: ↑homocysteine, nl MMA • **↓B12**: ↑homocysteine, ↑MMA (↑anti-IF Ab, ↑gastrin if pernicious anemia; falsely nml B12 possible) • Copper deficiency • **Early myeloproliferative d/o** **Non-megaloblastic**: MCV usually <110 • **Cirrhosis, EtOH** • **Reticulocytosis**: lysis or bleed • **Hypothyroidism** • **MDS** (refractory anemia) **& MM** **Meds**: antifolates, pur/pyr analogs, AEDs, HAART, AraC, Hydrea, others

DESTRUCTION/LOSS (RI >2%)

Extrinsic (to RBC)	**Intrinsic** (to RBC)
MAHA (-DAT, +schisto): see *Thrombocytopenia* • Smear (≥2 schisto/HPF), plt ~25K, ↑LDH, ↑indirect bili, ↓hapto **Immune (+DAT, +spherocytosis)**: Ab- and/or complement-mediated • **Warm autoimmune** (CLL, HIV, lymphoma, SLE): +DAT anti-IgG/C3 • **Cold autoimmune** (EBV, lymphoid malig, mycoplasma): +DAT anti-C3 • **Drugs** (PCN, cephalosporins)**, alloimmune** (hemolytic transfusion rxn) **Non-immune (-DAT)**: • **Infection**: Babesia, Malaria, Bartonella, C. perfringens, H. flu (type B) • **Toxin**: lead, copper (Wilsons), insect/spider/snake bites, hypotonic infusion • **Hypersplenism**: many; massive SM usually heme malig or infection • **Vitamin E** • **Mechanical trauma**: mechanical valve, aortic stenosis	**Hereditary**: • **Hb** disease (SS, HbC, thal): Hb electrophoresis • **Enzyme deficiency** (G6PD, PK): *G6PD levels often nml in attack*; check 4w later & repeat in 3mo if ⊖ • **Membrane defect:** spherocytosis, elliptocytosis **Acquired (new onset)**: • **PNH** (paroxysmal nocturnal hemoglobinuria): flow cytometry ± FLAER for GPI anchor, smear nml, UA (Hgb/hemosiderin), thrombosis (intra-abd/cerebral) **Acute blood loss**: GI blood loss, hematoma
Intravascular: ↑↑LDH, ↓↓hapto, hemoglobinemia & -uria; **Extravascular**: ↑indirect bili ± ↑LDH ± ↓hapto (if free Hb escapes spleen)	

Ellen Kendall

IRON DEFICIENCY ANEMIA (NEJM 2015;372:1832; Blood 2019;133:30)

- **Etiology**: ↑loss due to chronic bleeding (PUD/UGIB [↑BUN w/o ↑Cr], LGIB/CRC, menses, parasites, intravascular hemolysis), ↑demand (Epo, pregnancy, blood donation), ↓intake (malnutrition) or ↓absorption (Crohn's, ↑pH [e.g. PPI], post-gastrectomy, Celiac)
- **Evaluation**: GI bleed eval, H. pylori; consider Celiac disease (esp. if not responsive to PO iron), menorrhagia hx. Calculate Fe deficit with Ganzoni equation (can also use .irondeficit in EPIC)
- **Treatment**: **PO 325mg $FeSO_4$QOD** (QOD ↑ absorp: Lancet Haematology 2017;4:e524). ~6w to correct anemia, ~3-6mo to replete stores. ↑absorp. on empty stomach, VitC may ↑, ↓w/ Ca foods, antacids. GI SE: constipation, epigastric pain, N/V
  - IV iron if ongoing heavy bleeding, CKD, malabsorption, IBD, intolerant to PO, or chronic CHF (NEJM 2009;361:2436). IV Iron at d/c following ADHF ↓risk of future HF hospitalizations (Lancet 2020;396:1895). Typical dose: **iron sucrose 100 – 300 mg per dose, repeated until total iron req met**. SE: n/v, pruritus, flushing, myalgia/arthralgia, CP; ⦸ by 48h. Anaphylaxis rare with modern products. Pt with inflammatory arthritis may have flare from IV infusion.

ANEMIA OF INFLAMMATION/CHRONIC DISEASE (NEJM 2019;381:1148; Blood 2019;133:40)

- **Etiology**: autoimmune, infection, malignancy, CHF, CKD, obesity, DM, aging, critical illness; inflammatory cytokines (IL-1, IL-6 & TNFα) → ↑hepcidin → ↑ferroportin internalized / degraded → ↓intestinal Fe absorption, ↓Fe & hepatic Fe mobilization
- **Time course**: usually 1-2mo to develop, but can ↓Hgb 2-3g/dL in 1-2d in acute illness
- **Treatment**: tx underlying disease. Fe if concomitant Fe deficiency.
  - **Erythropoiesis stimulating agents (ESA)**: FDA-approved for anemia a/w CKD & HIV on HAART. Controversial in cancer pts (JCO 2019;37:1336). Evidence against use in CHF (NEJM 2013;368:1210). Maintain Tsat ≥20%, ferritin ≥100 for EPO therapy

MACROCYTIC / MEGALOBLASTIC ANEMIA (MCV ≥100μm^3)

- Review meds, if without megaloblastic changes (hyperseg PMN): consider thyroid, liver, nutritional causes, MDS, reticulocytosis
- ↓**Folate** ("foliage"), **3mo** stores; ↓intake (EtOH, elderly), ↓absorption (Celiac, jejunum), ↑demand (pregnancy, hemolysis, malignancy), meds (MTX, TMP, AEDs). When severe a/w hemolysis & pancytopenia; ↑homocysteine, MMA nml
  - **Tx**: 1-5mg PO qd (can worsen B12 deficiency and associated neurologic complications if not replete)
- ↓**B12** ("beef"), **3y** stores; ↓intake (EtOH, vegan), pernicious anemia (Ab to intrinsic factor (IF), gastric parietal cells), ↓absorption (gastrectomy, Celiac, Crohn's, PPI, chronic pancreatitis), ↑competition (SIBO, tapeworm); when severe a/w pancytopenia & subacute combined degeneration (dorsal columns, corticospinal tract) w/ dementia, ataxia, paresthesia
  - **Labs**: check homocysteine/MMA if B12 borderline (200-350). Consider anti-IF Ab if homocysteine/MMA ↑ or if B12 <200
  - **Tx**: 1-2mg PO B12 qd vs IM dosing (depending on if symptomatic anemia, neuro sx, malabsorption). Post-tx, neuro sx start to improve 3mo-1y (NEJM 2013;368:149)

AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA) (NEJM 2019;381:647; Blood 2017;129:2971)

- **Warm AIHA**:
  - Etiology: antibody-mediated, often **idiopathic**, less common CLL/lymphoma/MM, ALPS, SLE, HIV, EBV, hep C, SARS-CoV-2, babesia, meds. Extravascular > intravascular hemolysis. Rule out other causes of hemolytic anemia
  - Dx: +DAT anti-IgG and/or C3d (typically IgG and panagglutinin). ↓haptoglobin, ↑LDH, ↑indirect bili, ↑reticulocytes.
  - Tx: transfusion for symptomatic anemia or Hgb <7, steroids, d/w blood bank. 2nd line: rituximab, splenectomy, mycophenolate
- **Cold agglutinin disease**:
  - Etiology: **Often associated with lymphoproliferative process, EBV, mycoplasma, autoimmune**. Hemolysis mediated by complement.
  - Dx: +DAT anti-C3d only and cold agglutinin titer
  - Tx: Tx underlying process, workup clonal lymphoproliferative disorder. If symptomatic, warm transfusions, plasmapheresis, rituximab, sutimlimab. Steroids/splenectomy not indicated.
- **Drugs**: both Ab & non-Ab-mediated; abx (PCN, cephalosporins, sulfa); NSAIDs; rasburicase (G6PD), anti-cancer meds, others
  - If +DAT but no hemolysis, think **drugs**, ↑↑**IgG** (IVIG/RhIg/myeloma), **CTD** (e.g., controlled SLE)
- **Other etiologies**: paroxysmal nocturnal hemoglobinuria (PNH), paroxysmal cold hemoglobinuria (PCH; anti-C3).

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

- Excessive inflammation/tissue destruction secondary to abnormal immune activation of macrophages and lymphocytes & cytokine storm
- **Workup: molecular testing or dx with** 5/8 of **fever**, ↑**spleen**, 2/3 **cytopenias**, ↑TG /↓fibrinog, ferritin ≥500 (usually >3k), ↑sIL-2R, hemophagocytosis in BM, spleen, or LN, low/no NK activity. Also ↑LFTs, hepatomegaly, ↑LDH, ↑D-dimer, ↓ fibrinogen, ↓ESR, ↑CXCL9. **H-score** for probability.
- **Consider evaluating for associated/underlying illness**: infection (pan-culture, viral titer/PCR: EBV, CMV, hepatitis, HSV, VZV, HIV, HHV-8, HHV-6, parvo, bartonella, leishmaniasis), malignancy, CAR-T, rheum, neuro (brain MRI, LP), genetic
- **Tx**: Depends on etiology. If acutely ill, consider dexamethasone +/- etoposide. Dexamethasone is steroid of choice as it crosses the blood brain barrier. Consider etoposide-based regimen or allogeneic HCT (ASH: Blood 2019;133:2465)

OVERVIEW (JAMA 2022;328;570)

- **Definitions**:
  - Sickle Cell allele: autosomal recessive βglobin gene A->T (Glu6Val) missense mutation
  - Sickle Cell Trait (SCT): heterozygous for HbS w/o aberrancy in partnered βglobin gene
  - Sickle Cell Anemia (SCA): homozygous for HbS
  - Sickle Cell Disease (SCD): any variant of an inherited hemoglobinopathy with formation of HbS leading to sickle shape of RBCs
  - HbSC disease: Equal amounts of HbS & HbC (greater loss of K^+ dehydrating RBCs & promoting sickling). Freq dehydration, relative to SCD retain splenic function & less hemolysis. Smear: target cell, HbC crystals, some sickled cells.
- **Epidemiology**: ~300K born with SCA per year worldwide. ~100K w/ SCD in U.S, 1.2K families in Boston area. ~7-8mil worldwide
- **Pathophysiology**: deoxygenated HbS polymerization → sickle shaped RBCs, impacts RBC membrane integrity, adherence to vascular endothelium → hemolysis-related endothelial dysfunction and vaso-occlusive events (VOE) which can affect any organ
- **Diagnostics**: baseline Hb electrophoresis and HPLC: tests to separate HbS from other variants (HbA, HbF, HbC)

CLINICAL MANIFESTATIONS

- **Acute Pain Episodes** (Complement Ther Med 2020; 49:102327):
  - Complication for which patients most commonly seek medical attention; frequency peaks between ages 19-39
  - Sx: severe pain, swelling, tenderness, HTN, N/V. Frequency peaks age 19-39. ↑risk when Hb >8.5 and ↓HbF.
  - Triggers: dehydration, infection, changes in the weather, stress, menses, EtOH. Over 50% w/o clear etiology.
  - Dx: no objective signs or lab values, patient report is the criterion standard
- **Acute Chest Syndrome**: #2 cause of hospitalization. Pulmonary arterial circ ↓O2 tension → ↑risk VOE. Complications including PNA, thromboses, fat embolism. NB: 50% preceded by or a/w acute pain episodes
  - Definition: new imaging infiltrate + pulmonary symptoms in a patient with SCD, freq. with fever, chest pain, cough
  - Dx: CXR, ↑WBC, r/o PE & MI
  - Tx: O2 goal >95%, antibiotics (CTX+azithro or FQ), adequate analgesia is critical to prevent splinting-sickling cycle, transfusions (simple vs exchange), bronchodilators
- **Other organ systems**:
  - 1) Splenic sequestration: 20% pts; acute 2g/dL ↓Hb
  - 2) Infection: given functional asplenia and hyposplenism, ↑risk of encapsulated org, defects in alternative complement pathway. If febrile, send BCx and cover empirically w/ CTX (+azithro if c/f acute chest; +vanc if HDUS or c/f meningitis)
  - 3) CV: major cause of death, CM (secondary to chronic anemia, hemosiderosis), ↑MI risk (even in absence of atherosclerosis)
  - 4) Neurologic: stroke (~1/4 of pts with SCA with experience a stroke by age 45) → neurocog impairment, epilepsy
  - 5) Hepatobiliary: acute hepatic ischemia, iron overload from frequent transfusions, pigmented gallstones
  - 6) Bone: ↑rate Vit D def & osteoporosis, osteonecrosis
  - 7) Heme: chronic compensated anemia (Hg 8-10), aplastic crisis, & hyper-hemolytic episode: rare; pain, fever, ↓Hb w/in 7-15d of transfusion; Tx: notify blood bank, hydration ± steroids, IVIG, rituximab, eculizumab
  - 8) Vascular/cutaneous: priapism, leg ulcers, pulmonary HTN, renal insufficiency, proliferative retinopathy

Severe complications of disease requiring urgent hematology consult to discuss red cell exchange: severe acute chest syndrome, stroke, multiorgan failure syndrome, myocardial infarction

MANAGEMENT

Sickle Cell Pager (p28439) for every admission, consult inpatient hematology for severe SCD-related complications (as above)

- Workup: CBC/diff, BMP, LFTs, coags, reticulocyte count, BCx, UA/UCx; CXR; special slide (polychromasia., sickle cells, Howell-Jolly)
- **All inpatients: VTE ppx, pain control,** O2 (SpO2 <92%), often IVF for acute pain episodes. **See Acute Care Plan**. Utilize Epic Order Set ("General Adult Sickle Cell Crisis").
  - **Pain control**: IV opioids within <1hr of ED arrival (see MGH ED protocol) ± fluids at 100-150 mL/hr IV ± NSAIDs (5-7 days; ketorolac ≤ 5 days; Blood Adv 2020;4:2656). If unknown prior dose, ask patient and consider IV morphine 0.1-0.15mg/kg ≤10mg or Dilaudid 0.02-0.05mg/kg (max 1.5mg). Once admitted, discuss transition to PCA with patient and pharmacy. Do not hold long acting PO opioids unless on a PCA with a basal rate. Avoid steroids (↑ rebound pain). Give aggressive bowel regimen ± methylnaltrexone. If uncontrolled, contact chronic pain for high dose PCA titration and to consider ketamine (MGH policy).
  - **Pruritis**: chronic (non-sedating antihistamine or 5-HT_3RA), inpatient consider continuous infusion ↓dose naloxone gtt (0.25 mcg/kg/hr), compatible for simultaneous admin w/ morphine. *Note: Avoid IV Benadryl in favor of PO*
- Neutral language: misperceptions interfere with management, biased language a/w poor pain control and ⊖ attitude to pt (JGIM 2018;33:685). Avoid stigmatizing terms, including: "sickler, freq. flyer, pain seeking" which foster bias and bidirectional mistrust (JAMA 2022;328;570).
- Transfusions: *Indicate Sickle Cell on Epic transfuse order for more extensive match.* Mechanisms of benefit include: dilute HbS, ↓Epo reducing production of new HbS cells, ↑SpO2. Indicated in stroke, multiorgan failure, acute chest, sequestration, peri-op. symptomatic or severe anemia (drop of hgb >2 from their baseline). No e/o benefit in acute pain episode (Br J Haematol 2015;171:288). Exchange > simple (risk of hyperviscosity). Judicious w/ transfusion (risk of clinically sig. iron overload if >15-20 RBC units) (Blood Adv 2020;4:327).
  - Iron chelators: deferoxamine (subcutaneous and IV), deferiprone and deferasirox (PO, poorly tolerated, toxic). Initiated ~1-2 years of chronic transfusions or ferritin >1000-1500 ng/mL.
- Outpatient: hydroxyurea (↑HbF; continue inpatient), folate/MVI, L-glutamine (↓ RBC oxidative stress; NEJM 2018;379:226), voxelotor (inhibits HbS polymerization; no improvement in VOEs or mortality; NEJM 2019;381:509), crizanlizumab (P-selectin antag, ↓RBC adhesion; approved for prevention of VOEs; NEJM 2017;376:429). Vaccines for encapsulated bacteria (Mening, HiB, Pneumo), HBV, flu, CoV-19. Consider prophylactic transfusions in patients with multiple episodes of acute chest despite maximal therapy. Consider SNRIs, amitriptyline, and pregabalin for chronic pain (Blood Adv 2020;4:2656).
- Other therapies: allogeneic BMT only curative option. Gene therapy targeting BCL11A (CRISPR use) (NEJM 2021;384:205).

THROMBOCYTOPENIA (Hematology 2012;2012:191)

Definitions: 100-150k mild, 50-99k mod, <50k severe. **Bleed risk**: <50k w/ surgery/active bleed, <30k w/ mild trauma, <10k spontaneous

↓Production	↑Destruction	Sequestration/Dilution
- Infection: sepsis, HIV/HCV, VZV/CMV/EBV, parvo, tickborne - Nutrition: EtOH, ↓B12, ↓folate - Drugs: abx, chemo (ASH Edu 2018;2018:576) - Neoplasm: MDS, BM infiltration, 1° heme - Other: hereditary, cirrhosis, aplastic anemia, some vWD	- Immune: ITP, SLE/APLS, RA, lymphoma, post-transfusion - Drugs: heparin, MTX, abx, AEDs, anti-GPIIb/IIIa, quinine - MAHA: DIC, TTP, HUS, mHTN, preeclampsia/HELLP - Mechanical: CVVH, CPB, ECMO, IABP, valves	- Hypersplenism - Hemangioma - Massive transfusion - Hypothermia - Gestational

Workup:

- H&P focused on bleeding (GI, GU, epistaxis, HA, mucocutaneous), etiology, timing of plt ↓. If new HA: consider CTH
- R/o alarming causes: HIT, TMA, catastrophic APLS. Identify common causes: infxn, drug, immune, nutrition, hypersplenism, MDS
- Initial labs: CBC, BMP, LFTs, coags, special slide, T+S, HIV, HCV, pregnancy test, citrated plt count (r/o pseudo-thrombocytopenia)
- If asymptomatic, mild (100-150k): history of risk factors (i.e. alcohol use), routine exam, CBC for other cytopenias, special slide, HIV/HCV testing, B12, folate (common cause of over-testing)
- If c/f MAHA (e.g. schistocytes on slide): add LDH, haptoglobin, DAT, retics, D-dimer, fibrinogen
- If c/f SLE/APLS: add ANA, lupus anticoagulant, anti-cardiolipin, anti-β2GP1
- If c/f BM disease: consult Hematology, consider BM biopsy

IMMUNE THROMBOCYTOPENIA (ITP) (Blood Adv 2019;3:3829; Blood 2017;129:2829; NEJM 2019;381:945)

Pathologic antiplatelet antibodies cause plt clearance and bind to megakaryocytes/progenitors, resulting in apoptosis and near-normal rate of platelet production. Defined by isolated plt <100k, **dx of exclusion – must exonerate other causes of thrombocytopenia**
Presentation: **Precipitous and sudden decline in platelet.** Asx or mucocutaneous bleeding; 10% of ITP has AIHA. Associated w/ H. pylori, HCV, HIV. Consider thrombopoietin level (may predict responsiveness to TPO receptor agonists (Am J Hematol 2018;93:1501-1508)).
Prognosis: <10% spontaneous resolution, up to 50% recover with 1st line tx. 1.4% risk of ICH, 9.5% risk of severe bleeding
Management: "response" = plt ↑2X to ≥30k within 3mo

- Plt ≥30k & asx/minor bleed: observe; consider steroids if elderly, comorbidities, on AC/anti-plts, upcoming procedures, & plt near 30k
- Plt 10k-29k: steroids ± IVIG, RhoGAM if RhD+; if not bleeding, DO NOT give plts (destroyed & ↓ Plt further) (Blood 2015;125:1470)
  - Steroids (takes 4-14d to work): dexamethasone 40mg/d x4d, methylpred 1g/d x3d, or prednisone 60mg/d x3w w/ taper
- Plt <10k: steroids + IVIG, consider romiplostim, do not give plts unless c/f bleeding
- Severe bleeding: Plt, IVIG, steroids (pulse-dose methylpred & dex), Amicar (0.1g/kg/30min→gtt 0.5-1g/h)/TXA, romiplostim
- Refractory/recurrent: ↑romiplostim dose, ritux, fostamatinib; last resort (>12m after dx) splenectomy (>50% effective, risk of relapse)

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) (Blood Adv 2018;2:3360; Blood 2017;129:2864; NEJM 2015;373:252)

IgG anti-PF4-heparin complex binds & activates plts, hypercoagulable state. Can occur with any heparin (UFH, LMWH, heparin flushes)
Types: HIT Type 1 (mild platelet drop no lower than 100k 1-2d from heparin exposure, not clinically significant) vs. HIT Type 2 (see below)
Presentation: 5-10d after exposure, ↓plt >50%, nadir 40-80k, thrombosis in 30-50% (skin necrosis, DVT/PE, arterial), GIB (~3%)

- Consider rapid-onset HIT if <24h with prior exposure within 100d; delayed-onset can present up to 3w after last heparin

Diagnosis/Management: Calculate 4Ts Score. (If incomplete information, may be prudent to err on side of higher 4T score. Recalculate for change in clinical picture). If 0-3: HIT unlikely (NPV 99%), OK to continue heparin. **If ≥4**:

1) **Stop heparin**, **reverse warfarin** (prevent skin necrosis), and **start non-heparin AC**. No plt transfusion unless severe hemorrhage
2) Send **anti-PF4**. Send **serotonin release assay (SRA)** (gold standard). Do not wait for results to do Step 1
   - PF4 neg: HIT unlikely; OK to resume heparin. PF4 OD ≥2, or OD ≥1.5 with 4Ts ≥6: HIT likely. Otherwise: decide based on SRA
3) Screen for DVT with upper/lower extremity ultrasound

- Duration of AC: if no thrombosis, until plt >150k (at least 4 weeks); if thrombosis, at least 3mo. Non-heparin AC options:
  - **Fondaparinux** (IV or SQ): for stable non-surgical patients, contraindicated if GFR <30, irreversible
  - **Argatroban** (IV): preferred in renal failure & surgical pts, monitor w/ chromogenic Xa (goal 20-40%)
  - **Bivalirudin** (IV): only approved for HIT undergoing PCI, preferred in liver failure
  - **PO Options**: **DOACs** for non-urgent AC, **warfarin** not until plt >150K for 2 consecutive days
- Add heparin to allergies, avoid in future & use other VTE ppx. If strong indication (e.g., bypass) small studies *suggest* no ↑ risk of HIT in pts with h/o HIT >100d prior *if* anti-PF4 now neg (NEJM 2001;344:1286; NEJM 2000;343:515). **Resolution of ↓Plt expected in ~7d**

THROMBOTIC MICROANGIOPATHY (TMA) (NEJM 2014;371:654)

Microthrombi → **MAHA** (↓Hb, ↑LDH, ↓haptoglobin, +schistos, -DAT), **↓↓plt** (consumption), **end-organ injury** (vascular occlusion)

- **Drug-induced (DITMA):** gemcitabine, oxaliplatin, quetiapine, quinine, tacrolimus, cyclosporine, bevacizumab, opioids
- **TTP** (Plt <30K): inherited/acq. *ADAMTS13* def. →vWF multimers →formation of plt microthrombi. S/Sx: purpura, GI sx, neuro sx; fever, AKI. Dx: PLASMIC score mod/high, lab testing of ADAMTS13 activity. Tx: **plasma exchange/FFP,** steroids, ritux. DO NOT transfuse to correct Plt unless severe bleed, though transfusion not a/w ↑ risk of mortality/CNS comp (Transfusion 2009;49;873).
- **HUS** (plt >30K)
  - **Shiga-toxin-mediated** O157:H7 *E. coli*, *Shigella* ("ST-HUS"). S/Sx: bloody diarrhea, severe AKI; severe neuro sx rare. Dx: stool ⊕ for organism or toxin; Tx: supportive (IVF, HD) (Blood 2017;129:2847)
  - **Complement-mediated** ("atypical HUS"): S/Sx: severe AKI + 20% w/ extra-renal sx (CNS, cardiac, pulm hemorrhage, panc.); Dx: complement genotyping, anti-complement Ab. Tx: plasma exchange; eculizumab (NEJM 2013;368:2169)
- **2° Etiologies**: DIC, infxn, malignancy, SLE/APLS, scleroderma, malignant HTN, HELLP, post-HSCT
- **Immediate Management:** if DITMA, d/c drug. Special slide (+schistos), c/s Heme if concerned and/or severe anemia/↓ Plt, monitor UOP (for renal impairment), consider complement (C3/C4) testing. 1st line: therapeutic plasma exchange, transfuse RBCs if symptomatic anemia, transfuse platelets for <20k or <50k with bleeding/pre-procedure.

Hematology

Eosinophilia

OVERVIEW (Am J Hematol 2022; 97:129; Hematology 2015;2015:92)

- **Eosinophilia**: AEC >500. **Hypereosinophilia**: AEC >1500. **Hypereosinophilic syndromes (HES)**: AEC >1500 + organ dysfunction
  - Eosinophils are quickly eliminated by steroids → eosinophilia may be unmasked as pts taper off chronic glucocorticoids
- Primary = due to clonal expansion (HES/leukemia). Secondary (reactive) = due to infection, atopy, meds, rheum dz, etc

Infections	**Helminthic**: strongyloides, toxocariasis, schistosomiasis, ascaris, filariasis, trichinellosis, hookworm, fascioliasis. **Fungal**: aspergillus (ABPA), coccidiomycosis, histoplasmosis. **Protozoal**: isospora. **Viral**: HIV, HTLV1/2
Malignancy	Primary HES (PDGFRA-assoc.), eosinophilic leukemia, CML, NHL, HL, mastocytosis; less common with solid tumors
Autoimmune	EGPA (see *Vasculitis*), PAN, eosinophilic fasciitis, RA, IBD, EoE, IgG4, sarcoidosis, GVHD, blistering disease
Allergic	Drugs (i.e. penicillins, cephalosporins, NSAIDs, ranitidine, aspirin, allopurinol, phenytoin, tetracyclines), DRESS, asthma/atopy, ABPA, hyper IgE syndrome, AIN, episodic angioedema (Gleich syndrome)
Misc	Adrenal insufficiency, cholesterol emboli syndrome, acute arterial thrombosis, radiation exposure, familial (Chr 5q mut)

WORKUP (Br J Haematol 2017;176:553; J Allergy Clin Immunol Pract 2018;6:1446; Hematology 2015;2015:92)

- **Hx**: meds/supplements (<6w), diet, travel, occupational exposures, atopy, infxn, malignancy, rheumatic dz, full ROS, Δ in sx
- **Exam**: assess for rashes, cardiac/pulmonary abnormalities, nasal/sinus involvement, LAD, hepatosplenomegaly, neuropathy
- **Initial diagnostics**: CBC/diff (repeat), special slide, BMP, LFTs, LDH, ESR/CRP
  - If AEC 500-1500: check troponin, B12/tryptase, CXR if clinically indicated
  - If AEC >1500, assess for HES: check U/A, CK, troponin, EKG, CXR, PFTs, CT C/A/P or PET (for adenopathy, organomegaly, masses, organ infiltration), tissue biopsy of affected organs; also B12, tryptase, serum Ig levels
- **Additional diagnostics** (as clinically indicated): Strongyloides serology, stool O&P, other parasitoid/fungal serologies; ANCA if c/f EGPA; ANA, RF, CCP if c/f rheum dz; ACTH/cort stim if c/f AI; IgE levels, allergy testing if c/f allergy; imaging/bronch; endoscopy if c/f EoE/EGE; TTE/CMR if c/f cardiac dz; periph. flow ± BMBx if c/f MPD or >1500 & no obvious 2° cause
- **When to suspect drug reaction:** isolated ↑Eos or w/ systemic illness (e.g. DRESS, hepatitis, AIN). PCN/cephalosporins common culprits. Suspect DRESS if new drug 2-8w prior, fever, rash, facial edema, LAD, ↑ LFTs, ± organ involvement, atyp. lymphs.

TREATMENT (Hematology 2015;2015:92)

- Urgent Tx: if cardiac, neuro, or thromboembolic complications, AEC >100,000/rapidly rising, or s/sx of leukostasis → 1mg/kg to 1g methylpred (+empiric ivermectin 200mcg/kg if potential Strongyloides exposure); obtain HES diagnostics above prior to initiating
- Non-urgent Tx: symptomatic or evidence of end-organ damage but does not need urgent Tx; see below for Tx by condition
- No Tx: if asymptomatic, no organ involvement, & no identified cause to treat, can monitor for resolution & organ damage

ORGAN-SPECIFIC PATHOLOGY

Cardiac: (Immunol Allergy Clin North Am 2007;27:457; JACC 2017;70:2363)

- Eosinophilic endomyocarditis: necrosis → thrombus formation (→ embolic events) → fibrosis → restrictive CM, valve involvement
  - May be due to hypersensitivity myocarditis, parasitic infections, malignancy, idiopathic HES
  - Dx: TTE (LV/RV apical dysfunction, restriction, intracardiac thrombi), cardiac MRI (+subendocardial LGE), endomycocardial bx
  - Tx: high dose steroids & remove culprit med (if hypersensivity), treat underlying disorder (parasite, HES)
- Eosinophilic coronary arteritis: rare complication of EGPA; may mimic ACS

Pulmonary: (Clin Microbiol Rev 2012;25:649; Chest 2014;145:883; J Allergy Clin Practice 2014;2:703)

- Acute eosinophilic PNA: <7d fever, cough, SOB; a/w smoking; ↑periph. Eos often absent; Dx: BAL Eos ≥25%; Tx: steroids
- Chronic eosinophilic PNA: >4w fever, cough, SOB, wt loss; a/w asthma; Dx: BL mid-upper lobe infiltrate; BAL Eos ≥25%; Tx: steroids
- Allergic bronchopulmonary aspergillosis (ABPA): asthma/CF c/b *recurrent exacerbations* w/ fever, malaise, brown mucus plugs; Dx: ↑Eos, ↑total IgE, ↑Aspergillus IgE & IgG, imaging w/ central bronchiectasis, UL/ML consolidations; Tx: steroids + itraconazole
- Loeffler syndrome: transient/migratory pulm. opacities, ↑Eos 2/2 helminth larvae; Dx: larvae in resp secretion (stool usually ⊖)

GI: (AGA EoE: Gastro 2020;158:1776; NEJM 2015;373:1640; Clin Rev Allergy Immunol 2016;50:175)

- Eosinophilic esophagitis (EoE): dysphagia, food impaction, GERD-like sx/refractory GERD, assoc w/ allergic conditions; Dx: EGD w/ bx, exclude other causes (GERD, motility d/o, Crohn's, infxn, CTD, etc.); Tx: dietary Δs, PPI, topical steroids (MDI/neb, PO liquid)
- Eosinophilic gastroenteritis (EGE): stomach/small bowel/colon ± esoph.; Sx: n/v/d, abd. pain, malabsorption (mucosal dz), poor motility/obstruction/perforation (muscular layer dx), ascities (serosa dz); Tx: dietary Δs, PO steroids

PRIMARY HYPEREOSINOPHILIC SYNDROMES (HES) (Am J Hematol 2022; 97:129; Hematology 2015;2015:92)

- **Myeloproliferative HES** (~20% of HES in US): acute/chronic eosinophilic leukemia; 80% pts have *FIP1L1-PDGFRA* fusion gene
  - Dx: anemia, thrombocytopenia, ↑tryptase, ↑B12, special slide (dysplastic eosinophils), BM Bx (fibrosis, hypercellularity)
  - Tx: if PDGDR+, imatinib ± steroids if cardiac sxs; if JAK2+, JAK2 inhibitor; if FGFR1+, chemo. 2nd line: sorafenib, midostaurin, or ponatinib.
- **Lymphocytic HES**: clonal T-cell expansion →↑IL-5 → ↑Eos. Often p/w skin/soft tissue involv., polyclonal hyper-IgG, ↑IgE. 5-25% progress to lymphoma (a/w Chr 6p deletion).
  - Dx: flow cytometry for aberrant Th2 type CD4 cells; Tx: steroids; 2nd line: IFN-α, hydroxyurea, anti-IL-5
- **Idiopathic HES/Hypereosinophilia of Uncertain Significance (HE_{us})**: eosinophilia w/o identified cause +/- organ involvement → consider ANCA-neg EGPA, suggested all pts get f/u to ensure no end-organ involvement even if asx at dx. Tx: Steroids only if sx.

HYPERCOAGULABLE STATES (NEJM 2017;377:1177) (ASH 2023 Guidelines)

Do not test at time of event or during anticoagulant therapy. If performed, should be **>2 weeks following d/c of anticoagulation**
Testing includes: Factor V Leiden, prothrombin gene mutation, protein C/S def, antithrombin deficiency, antiphospholipid Abs*

*[**Caveat in someone with compelling history there may be benefit to testing for APLS (serologies only) in the setting of acute clot as it may change management**]

	Do not test for thrombophilia	Test for thrombophilia
Patients with established VTE	- **Unprovoked VTE (warrants indefinite AC)** - VTE provoked by surgery - VTE provoked by other clear predisposing medical syndrome (nephrotic syndrome, MPN, HIT)	- VTE provoked by nonsurgical major transient risk factor (e.g. admission for PNA) or OCP/pregnancy/PP *[controversial]* - Cerebral/splanchnic VTE (+ test JAK2, PNH in hepatic/PVT) - VTE in patient < 45y **or** with 1st deg relative w/ VTE < 45y - Recurrent or multiple thromboses - Arterial thrombosis (test for APS) - Warfarin-induced skin necrosis (test for protein C deficiency)
Patients without VTE – special situations	- Females considering OCP/HRT without FHx thrombophilia - Patients with cancers at high risk of VTE (Khorana score) → thromboprophylaxis	- Females considering OCP/HRT or planning pregnancy **if + FHx high-risk thrombophilia** - Patients with cancer at low/intermediate risk of VTE and undergoing tx **if +FHx VTE**

INHERITED CONDITIONS		
Condition	**Clinical Pearls**	**Testing**
Factor V Leiden	- Most common inherited cause of hypercoagulability	- APC resistance assay (reliability iso heparin products depends on assay) → reflex FVL genetic test
PTG mutation	- 2nd most common cause; ↑prothrombin (FII)	- PCR for PTG G20210A mutation (most common)
Protein C/S deficiency	- Activated protein C/S inactivate FVa and FVIIIa; ↓level (more common) or function leads to hypercoagulability - A/w warfarin-induced skin necrosis (screen if hx)	- Free protein C/S functional assays - ↓ by acute thrombosis, VKA, liver dz, DIC, chemo, uremia (Prot C), pregnancy/OCP/nephrotic sx (Prot S) - ↑ by DOAC (Prot C/S), HLD and nephrotic sx
Antithrombin III deficiency	- ↓level or function - Heparin works via ATIII to inactivate FIIa and FXa; if ATIII defic., will be heparin-resistant & require ↑doses	- ATIII functional assay assessing FXa inhibition - ↓ by acute thrombosis, UFH/LMWH, liver dz, nephrotic; ↑ by DOAC, direct thrombin inhibitors
ACQUIRED CONDITIONS		
Antiphospholipid syndrome (APLS)	- **Primary** or **secondary** to SLE/other autoimmune dz - **S/Sx**: Unexplained venous/arterial thrombosis (esp. in young pts), adverse pregnancy outcomes, livedo reticularis/racemosa, valvular dz, ↓ platelets - **Catastrophic APS:** ⊕ aPL w/ 3+ organ thromboses in <1w, mortality ~50%. Tx: AC + steroids + TPE or IVIG	- Lab criteria: ⊕ LA, anti-cardiolipin, or anti-β2 glycoprotein >2x ULN, twice **12w apart** - LA unreliable on AC (false ⊕) and acute thrombosis (false ⊖); anti-CL and β2GP not affected - ⊕ aPL Ab can be seen in infx, rheum, malig, meds - False ⊕ VDRL (NEJM 2018;378:2010)

COAGULOPATHY (NEJM 2014;370:847)

Disorders of **1° hemostasis** (↓platelet # or function, VWD → mucocutaneous bleeding, petechiae, menorrhagia) or **2° hemostasis** (factor deficiency/↓activity → deep tissue bleeding, joint, organ, brain; prolonged PT/PTT)

- Rule out **artifact**, **anticoagulant use**, or **systemic disease** (cirrhosis, DIC, abx, malnutrition, renal disease, cancer)
  - Consider diseases affecting vascular function (e.g. HHT, scurvy, EDS)
- If prolonged PT/PTT and etiology is not clinically apparent, order **mixing study** w/ normal plasma (JAMA 2016;316:2146)
  - If PT/PTT corrects: supports **clotting factor deficiency** (confirm w/ factor specific assays)
  - If no/partial correction: supports **presence of inhibitor** (confirm w/ inhibitor specific assays)
    - Types: drugs (e.g. heparin), acquired factor inhib (VIII, V>>IX, XI; autoimmune d/o, malig), nonspecific inhib (e.g. LAC)
  - If work-up is unrevealing, consider VWD testing, platelet function testing, thrombin time (TT), fibrinogen, factor XIII
- Tx: replace missing factor, eliminate inhibitor (immunosuppressants), treat underlying condition

Hemophilia: most common severe bleeding disorder, X-linked. Caused by Factor VIII (Hemophilia A) or Factor IX (Hemophilia B) deficiency →reduced clot formation and stabilization →bleeding (joint damage from recurrent bleeds common cause of morbidity)

- Dx: **↑PTT** (can be normal in mild def) → 1:1 mixing study (if PTT corrects = factor def)→factor specific assay to distinguish A and B
- Tx: Concentrates of FVIII/FIX ppx for bleeding events or on-demand w/ bleeds. Emicizumab (bispecific ab which functions like Factor XIII) approved for prophylaxis in Hemophilia A. Multiple novel gene therapies currently under investigation (Blood 2019;133:389).

Coagulation Defect	Normal aPTT	Prolonged aPTT
Normal PT	**Platelet dysfunction** (VWD, other platelet disorders), ↓Factor XIII	**Intrinsic pathway**: ↓VIII, IX (hemophilia), XI (Ashkenazi); VWD; ↓XII, PK, HMWK (no bleeding); LAC (prothrombotic)
Prolonged PT	**Extrinsic pathway**: ↓Factor VII, warfarin, liver disease, Vit K deficiency	**Common pathway**: liver disease, DIC, Vit K deficiency, warfarin. Rarely common pathway deficiency/inhibitor

DIC: massive activation of coag cascade caused by various inflamm. etiologies (sepsis, CA, obstetric complications, trauma, pancreatitis). Consumption of coag. factors → **bleeding**, microvascular **thrombosis**, MAHA, organ dysfunction (kidneys, lungs, CNS, adrenal)

- Dx: **↑PT/PTT, ↑D-dimer, ↓fibrinogen, ↓plts, +schistos, ↑LDH, ↓hapto** (often normal coags in chronic DIC). Can differentiate DIC from liver dz w/ ↓FVIII (FVIII present in endothelium, not liver), DIC score
- Tx: treat underlying cause, transfuse plts if <10k, cryo if fibrinogen <100, FFP if INR >2. Amicar contraindicated generally.
  - If severe bleed: plts <30 or 50 and Fibrinogen <150

Hematology

Anticoagulation Agents

ORAL AGENTS (ASH: Blood Adv 2018;2:3257; CHEST: Chest 2021;160:2247)

Agent	Dosing	Bridging/Switching/Reversal
Warfarin (Coumadin) - Vitamin K antagonist: inhibits vitamin K-dependent gamma-carboxylation of Fs II, VII, IX, X, & Protein C+S - $t_{1/2}$ 40h (variable)	- Initiation: 5mg qd x2d; frail, HF, kidney/liver dz: consider 2.5mg; BMI >40: consider 7.5mg - Adjust by INR, which lags 48h behind dose Δ Monitoring: (UW Dosing Nomogram) **INR < goal**: ↑by 5-15% or consider booster dose **INR at goal**: no change **INR between 0.1 and 1.0 above goal**: ↓by 5-15%, consider holding a dose **INR >1 above goal**: hold until INR at goal, restart but ↓ by 10-20% **If overlap with direct thrombin inhibitor**: check chromogenic FXa: goal 20-40%	Bridging: (see below to bridge from parenteral AC): To parenteral AC: start IV w/o bolus when INR <2 *Reversal for life-threatening/intracranial bleed*: (Ellucid) 1) Vit K 5-10 mg IV over 10-20m 2) 4-factor PCC/Kcentra over 10m if INR >2 (≥1.5 in ICH) *MGH dosing*: Kcentra 1500u, follow INR q30m w/ pharm *Non-MGH dosing:* INR 2-4: 25u/kg (max 2500u), INR 4-6: 35u/kg (max 3500u), INR >6: 50u/kg (max 5000u) *If Kcentra not available, give 2U FFP by rapid infusion.* *Reversal without active bleeding*: INR >10→ Vit K PO 2.5-5mg INR 4.5-10→ Vit K PO 1-2.5mg if ↑risk of bleeding INR <4.5→ no reversal, hold warfarin
Dabigatran (Pradaxa) - Direct thrombin (IIa) inhibitor, $t_{1/2}$ 12-17h - 80% renal clearance - P-gp substrate - S/e: ↑dyspepsia, ?↑coronary events	- **Non-valvular AF**: 150mg PO BID if GFR >30, 75mg PO BID if GFR 15-30 (RE-LY, NEJM 2009;361:1139); some use 100mg PO BID dose if high bleeding risk - **VTE**: 150mg PO BID *after 5d UFH/LMWH* (RE-COVER, NEJM 2009;361:2342) - **PPX**: 110mg x1 then 220mg PO QD (RE-NOVATE II, Thromb Haemost 2011;106:721)	Bridging/switching: To parenteral AC: start 12h after last dose (24h if CrCl <30). From parenteral AC: start <2h before next dose. To warfarin: start 3d before dabigatran ⃠ if CrCl ≥50; 2d if CrCl 31-50, 1d if GFR 15-30; bridge PRN. From warfarin: hold warfarin and start dabigatran when INR < 2 Reversal if life threat.: can be dialyzed (Ellucid) - Idarucizumab 5g (RE-VERSE, NEJM 2017;377:431)
Rivaroxaban (Xarelto) - Direct Xa inhibitor - $t_{1/2}$ 5-9h; 11-13 in elderly - 66% renal clearance - Avoid with CYP3A4 and P-gp dual inhibitors	- **Non-valvular AF**: 20mg PO QD if GFR >50, 15mg if GFR 15-50 (ROCKET AF, NEJM 2011;365:883) - **VTE**: 15mg PO BID x21d, then 20mg QD. After 6mo, consider ↓ to 10mg QD if ongoing risk for VTE (NEJM 2010;363:2499; NEJM 2012;366:1287; NEJM 2017;376:1211) - **PPX**: 10mg PO QD (MAGELLAN, NEJM 2013;368:513)	Bridging/switching: (J Thromb Thrombolysis 2016;41:206) - To parenteral AC: start when next DOAC dose due - From LMWH/fonda: start w/in 0-2h of next dose - From UFH: start immediately after drip stops (for **edoxaban,** start 4h after stopping UFH) - From warfarin: • Start **rivaroxaban** when INR <3 • Start **apixaban** when INR <2 • Start **edoxaban** when INR ≤2.5 - To warfarin: (Note: all ↑INR) • **Rivaroxaban/apixaban**: stop, start warfarin, and use parenteral agent until at therapeutic INR • **Edoxaban:** cut edoxaban dose by ½ and begin warfarin, ⃠ edoxaban once INR ≥2 - DOAC to DOAC: start when next dose due Reversal if life-threat.: not dialyzed off (Ellucid) - Andexanet alfa (recombinant FXa): bolus → 2h gtt (NEJM 2015;373:2413; NEJM 2019;380:1326)
Apixaban (Eliquis) - Direct Xa inhibitor - $t_{1/2}$ 12h - lower renal clear. (25%) (*can use in ESRD*)	- **Non-valvular AF**: 5mg PO BID, 2.5mg BID if 2/3: Cr ≥1.5, Wt ≤60kg, age ≥80; some use 2.5mg BID if CrCl 15-29 (ARISTOTLE, NEJM 2011;365:981) - **VTE**: 10mg BID x7d, then 5mg BID x6mo; after 6mo, consider ↓ to 2.5mg BID (NEJM 2013;369:799 & 368:699) - **PPX**: 2.5mg BID (NEJM 2009;361:594)	
Edoxaban (Savaysa) - Direct Xa inhibitor - $t_{1/2}$ 10-14h - 50% renal clearance - Avoid if CrCl >95 or <15 - P-gp substrate	- **Non-valvular AF**: 60mg PO QD; 30mg if CrCl 15-50 or wt ≤60kg; do not use if CrCl>95 (ENGAGE AF, NEJM 2013;369:2093) - **VTE**: 60mg QD *after 5d UFH/ LMWH*, 30mg QD if CrCl 15-50, ≤60kg, or taking P-gp inhibitor (NEJM 2013;369:1406)	

PARENTERAL AGENTS

Agent	Dosing/Monitoring	Bridging/Switching	Reversal	Other
Heparin (UFH) - Binds & activates ATIII → inactivates Xa & IIa - $t_{1/2}$ 60-90min	- **ACS**: 60U/kg → 12U/kg/h; PTT 63-83 - **VTE**: 80U/kg → 18U/kg/h; PTT 70-100 - **PPX**: 5,000U SC q8-12h - Monitoring: PTT; anti-Xa (goal 0.3-0.7) if baseline ↑PTT or high doses; ACT if ↑↑)	- To LMWH: give LMWH & ⃠ UFH at same time - To warfarin: ⃠ UFH once therapeutic ≥2d	- Protamine: 1mg per 100U heparin or 1mg LMWH (max 50mg). 60% reversal for LMWH, most effective if last dose within 8h - Do NOT give FFP (has ATIII, which potentiates AC effect)	- Preferred in renal failure (CrCl <30), peri-procedure, poor absorption, pregnancy
Enoxaparin (LMWH, Lovenox) - Binds & activates ATIII→inact. Xa>>IIa - $t_{1/2}$ 4.5-7h	- **ACS/VTE**: 1mg/kg BID; QD if GFR <30 - **PPX**: 40mg SC QD; 30mg BID if ↑↑risk; ↑30% if BMI ≥40; 30mg QD if GFR <30 - Monitoring: not routine; can check anti-Xa 4h after 4th dose, goal 0.5-1.0	- To UFH: ⃠ LMWH & start UFH w/o bolus 1-2h before LMWH dose due - To warfarin: ⃠ LMWH once therapeutic INR ≥2d		- Acute VTE: LMWH > UFH (Cochrane Rev 2017) - Prolonged $t_{1/2}$ in renal failure
Fondaparinux (Arixtra) - Binds & activates ATIII→inact. Xa only - $t_{1/2}$ 17-21h	- **VTE**: <50kg → 5mg QD | 50-100kg → 7.5mg QD | >100kg → 10mg QD - **PPX**: 2.5mg SC QD - CrCl <30: contraindicated - Monitoring: not routine; can check 4h anti-Xa	- To warfarin: ⃠ fonda. once therapeutic INR ≥2d - To UFH: start UFH (no bolus) 1-2h before due - From UFH: start 1h after UFH ⃠	- No reversal agent	- ↑aPTT at therapeutic doses - If CrCl 30-50, consider Δ agents
Argatroban - Direct IIa (thrombin) inhibitor - $t_{1/2}$ 45min	- **HIT**: 1-2mcg/kg/min - Monitoring: PTT, goal 1.5-3x baseline - Caution in critically ill, cardiac dysfunction, liver disease	- To warfarin: ⃠ once chromogenic factor Xa 20-40% (argatroban ↑INR)	- No reversal agent	

Factor XI/XII inhibitors under investigation (Blood 2022;1:495): antisense oligonucleotides (ASO), antibodies (abelacimab NEJM 2021;385:609, osocimab, small molecules (milvexian, asundexian)

Hematology

Anticoagulation Management

Choosing An Anticoagulation Agent

Guidelines: CHEST for VTE: Chest 2021;160:2247, ASH for VTE: Blood Adv 2021;5:927, ASCO for VTE in CA: JCO 2020:38;496; ACC/AHA/HRS for AF: JACC 2019;74:104, CHEST for AF: Chest 2018;154:1121; AHA/ACC for Valvular HD: JACC 2021;77:e25

VTE	**Obesity**	**Avoid DOAC** if BMI ≥45 or wt ≥150kg, use warfarin (Circulation 2024;149). If use, ✓peak/trough (ISTH: JTH 2021;19:1874)
	Active Malignancy	**Apixaban** (CARAVAGGIO, NEJM 2020;382:1599), **edoxaban** (NEJM 2018;378:615), **rivaroxaban** (JCO 2018;36:2017), **LMWH** > warfarin (CLOT, NEJM 2003;349:146). Prefer apix or LMWH in GI/GU CA w/ intralum. lesions (edox/rivarox ↑bleeding risk). **DOAC > LMWH** for **short-term** VTE tx, **either for long-term**. Apix/rivarox **ppx** ↓VTE in high-risk outpts, suggest in mod-risk: consider if Khorana ≥2 (AVERT, NEJM 2019;380:711; CASSINI, NEJM 2019;380:720). LMWH ppx OK in high-risk outpts
	Recurrent	**If on non-LMWH**: switch to LMWH. **If on LMWH**: increase LMWH by 1/4-1/3 of current dose and check Xa level
	All Others	**DOACs** > warfarin > LMWH
AF	**Non-valvular**	**DOACs** > warfarin for stroke risk, mortality, and bleeding risk
	Valvular	**Warfarin** if mod/severe MS (regardless of CHADS2VASC)
	+ PCI	**Dual** (P2Y12i+OAC) v **triple therapy** (+ASA): dual w/ ↓bleeding, likely no ↑events (Annals 2020;172:474; EHJ 2019;40:3757)
		Dual therapy: **DOAC + clopidogrel** x-6-12mo. Rivaroxaban 15mg qd (some use 20mg) (PIONEER AF, NEJM 2016;375:2423) & dabigatran 150mg BID (RE-DUAL PCI, NEJM 2017;377:1513) in guidelines, also data for apixaban (5mg BID unless 2.5mg indicated) (AUGUSTUS, NEJM 2019;380:1509) & edoxaban 60mg QD (*though didn't ↓bleeding v VKA) (ENTRUST-AF PCI, Lancet 2019;394:1335). Warfarin + clopi or ticag also option (WOEST, Lancet 2013;381:1107). Ticag may be used in-hospital or if very high thrombotic risk. After 12mo, can likely Δ to OAC alone (AFIRE, NEJM 2019;381:1103)
		If triple therapy chosen (high thrombotic/low bleed risk), typically d/c ASA & transition to P2Y12i+OAC therapy at 1-6 wks
Valve	**Mechanical**	**Warfarin (+ASA for aortic On-X valve)**. DOACs not approved. INR goal for AVR = 2.5 (3 if +AF, VTE, etc.); MV/TV = 3
	Bioprosthetic	SAVR: **Warfarin** (INR 2.5) + **ASA** 3-6mo→**ASA**. TAVR: **ASA/clopi** 3-6mo→**ASA**. If AF/VTE, OAC+clopi→OAC (evolving)
APLS		**Warfarin**. Warfarin > rivaroxaban in high-risk APLS (TRAPS Blood 2018;132:1365; AIM 2019; 171:685)
CAD	**ACS** (⦸ PCI)	Very low dose rivaroxaban (2.5mg BID) added to ASA/clopidogrel→↓CV mortality but ↑major bleeding (NEJM 2012;366:9)
	2° prevention	Very lose dose rivaroxaban (2.5mg BID) + ASA → ↓MACE vs. ASA alone; ↑major bleeding but no Δ in ICH or fatal bleeding (COMPASS, NEJM 2017;377:1319). Can consider if high risk for events & low bleeding risk
	s/p PCI	**12 mo DAPT**, new research w/ 1-3 mo DAPT+12 mo clop non-inf to 12 mo DAPT (STOPDAPT-2, JAMA 2019;321:2414); can integrate DAPT score into clinical decision making

Anticoagulation Bridging

Guidelines: ACC: JACC 2017;69:871; ASH: Blood Adv 2018;2:3257; CHEST: Chest 2022;162:E207

Indication	AF		VTE		Mechanical Valve	
Thrombotic Risk	**Risk Factors**	**Bridge?**	**Risk Factors**	**Bridge?**	**Risk Factors**	**Bridge?**
High	- CHA_2DS_2-VASc ≥7 (or CHADS2 5-6) - CVA/TIA, or systemic embolism <3mo - Rheumatic valvular dz	Yes, unless major bleed/ICH <3mo	- VTE <3 mo - Severe thrombophilia: protein C/S or ATIII def, APLAS, multiple abnormalities	Yes	- Any mechanical MV - Caged ball/tilt disc AVR - Any mechanical valve w/ CVA/TIA <6mo	Yes
Moderate	- CHA_2DS_2-VASc 5-6 (or CHADS2 3-4) - CVA/TIA or systemic embolism >3mo	Likely bridge if prior CVA/TIA and if no ↑risk of bleeding	- VTE 3-12mo - Recurrent VTE - Active malignancy - Non-severe thrombophilia: heterozygous factor V Leiden, PTG mutation	No	- Bileaflet AVR w/ ≥1 CVA risk factor: age >75, AF, prior CVA/TIA, HTN, DM2, CHF	Consider against risk of procedural bleeding (UpToDate table)
Low	- CHA_2DS_2-VASc ≤4 (or CHADS2 0-2) - No prior CVA/TIA or systemic embolism	No	- VTE >1y & no other risk factors	No	- Bileaflet AVR w/o AF or CVA risk factor	No

- **BRIDGE** trial (NEJM 2015;373:823) demonstrated no difference in arterial embolism but ↑risk of bleeding w/ bridging in pts with AF undergoing invasive procedure requiring interruption of VKA (*NB*: excluded pts w/ mech. valves, stroke/TIA <3mo, major bleeding <6w, CrCl <30, plt <100k)
- Bridging Vitamin K Antagonist (VKA) w/ UFH or LMWH (prefer LMWH if kidney function allows):
  - Stop VKA 5d prior to procedure if therapeutic INR. Start UFH or LMWH when INR <2
  - Stop UFH 4-6h prior to surgery and LMWH 12 or 24h prior to surgery (depending on dosing interval)
  - Restart UFH/LMWH at 24h postop. if low postprocedural bleeding risk or 48-72h if high risk. ⦸ when INR >2
  - Resume VKA w/in 24h postop if no bleeding complications (will not ↑early bleeding risk because effect takes 24-72h)
- DOACs: no bridging required; most can be stopped 24-72h prior to surgery, depending on procedural bleeding risk & renal function

Drug	High Bleed Risk*		Low Bleed Risk*	
	CrCl >50	**CrCl <50**	**CrCl >50**	**CrCl <50**
Dabigatran	≥48h (4 doses)	≥96h (8 doses)	≥24h (2 doses)	≥48h (4 doses)
Rivaroxaban	≥48h (2 doses)	≥48h (2 doses)	≥24h (1 dose)	≥24h (1 dose)
Apixaban	≥48h (4 doses)	≥48h (4 doses)	≥24h (2 doses)	≥24h (2 doses)
Edoxaban	≥48h (2 doses)	≥48h (2 doses)	≥24h (1 dose)	≥24h (1 dose)

*For bleeding risk stratification use procedural bleeding risk + HAS-BLED score.

- If low bleeding risk, can resume 24h after procedure. If high bleeding risk, wait 48-72h. If NPO or more procedures: UFH/LMWH.

See *Peri-Procedural DOAC Management* for MGH-specific peri-procedural guidance for cardiac cath. lab & IR procedures

Maggie Selesky

Hematology

Transfusion Medicine

Transfusion Medicine Terminology

- **ABO typing**: front type: **A/B antigens** (pt's RBC + reagent anti-A or B); back: anti-A or B in plasma (pt's plasma + reagent RBCs)
- **Rh(D) typing**: tests for **D antigen** on RBC (pt's RBC + reagent anti-D) – *NB: anti-D is not a naturally occurring antibody*
- **Screening** (T&S): tests for **unexpected antibodies** in pt's plasma (pt's plasma + **screening** RBC + Coomb's reagent), "active" **x3d**
- **Crossmatching** (T&C): final confirmation test by mixing pt's plasma & **donor** RBC; performed just prior to transfusion
- **Direct antiglobulin test** (DAT/Coomb's Test): tests for Ab or complement on RBCs (RBCs + Coomb's reagents [anti-IgG, anti-C3])

Blood Products

Product	Description	Indications	Notes
Red Blood Cells	1U ~ 330cc Processing 1. Leukocyte reduction 2. Irradiation 3. Washing (rarely)	- Hgb <7 (NEJM 2014;371:1381; NEJM 2013;368:11) - Hb < 7.5 if cardiac surgery (JAMA 2023;1892:1902) - Hgb <8 if CAD, ortho surgery (JAMA 2021;325:552) - Hgb <10 if acute MI (NEJM 2023;389:2446) - Acute hemorrhage (>15% intravascular volume) - AIHA (no specific Hgb threshold) - Sickle cell disease (see *Sickle Cell Disease*)	- Each unit: Hct ~55% - **1U ↑Hgb ~1** - Rate: if active hemorrhage, give over 60-90min
Platelets	1U = 6pk = 300cc Types 1. Apheresis platelets derived from 1 donor 2. Pooled platelets from multiple donors Processing 1. Leukocyte reduction 2. Irradiation	- <10k: PPX spont bleeding (NEJM 1997;337:1870), antifibrinolytics in refractory thrombocytopenia in CA - <50k: active major bleed, intra- or post-op bleed, ppx prior to invasive procedures (<30k bedside procedures) - <100k: post-bypass bleed, ICH/ophthalmic (no data) - ITP: only if life-threatening CNS/GI/GU bleed (often preceded by wet purpura, mucus membrane bleeding)	- Response at 30-60m: **1U ↑PLT ~30K** - No evidence that apheresis > pooled plts - No evidence that platelets reverse anti-platelet agents (Lancet 2016;387:2605) - CI: TTP/HUS, HIT
Fresh Frozen Plasma	1U = 250cc Typical starting dose 2U Non-cellular portion of blood containing all coag factors; separated and frozen after collection	- Active bleed d/t deficiency in one or more coag. factors - ALF: consider for ↓plt or ↑INR only if bleed or pre-op - Cirrhosis: **cryo preferred**, treating INR w/ FFP ↑bleeding due to ↑portal pressures, has prothrombotic effect (J Thromb Haemost 2021;19:664) - Warfarin reversal: Vit K>PCC>FFP (Circ 2012;125:2944) - Trauma, DIC, congenital TTP (for ADAMSTS13) - Ppx prior to bedside invasive procedures for INR >2.0 (low quality evidence [Cochrane 2019:11:CD012745])	- Response: **2U ↑coag activity ~10%** - Max correction: **INR 1.7** - Effect <6h due to short $t_{1/2}$ of FVII - Potentiates effect of heparin with ATIII
Cryo-precipitate	10U = 150cc Contains factor VIII, factor XIII, VWF, and fibrinogen	- Fibrinogen <100-150: 50-100mg/dL give 10U; <50 give 20U - Massive transfusion w/ ↓fibrinogen or abnl ROTEM/TEG - Complex cardiac surgery (JAMA 2017;217:738) - Postpartum hemorrhage (Br J Anaesth 2015;114:623) - DIC, uremia if DDAVP ineffective, FVIII deficiency, VWD - Cirrhosis: fibrinogen <100-120 or c/f dysfibrinogenemia	- 10U cryo should ↑fibrinogen ~85mg/dL - Fibrinogen $t_{1/2}$ 3-5d - FVIII or vWF replacement: cryo is last resort therapy
Coagulation Factors	VIII, IX, rFVIIa, ATIII; combo: II+IX+X (Profilnine); PCC = II+VII+IX+X (Kcentra), FEIBA (anti-inhib. complx), vWF/FVIII (Humate-P)	- Coagulation factor deficiency/inhibitor - Von Willebrand's disease (Humate-P, NovoSeven) - VKA reversal (IV Vit K first, for severe bleed PCC > FFP)	- Blood Transfusion Service approval required - S/E: allergic rxn, thrombosis
Antifibrinolytics	Contain Lysine derivatives that bind to plasminogen to ↓fibrinolysis and ↑hemostasis Types (topical, PO, IV): Aminocaproic acid (Amicar), Tranexamic acid (TXA)	- Trauma (Health Tech 2013;17:1) - Postpartum hemorrhage (Lancet 2017;389:2105) - Cardiac surgery (NEJM 2017;376:136; J Thor C Surg 2019;157:644), ECMO - Cirrhosis: when hyperfibrinolysis suspected (see *ESLD)* - Major ortho surgery, plt refractoriness in HLA alloimmunization, closed space bleeding, coag factor inhibitor	- Amicar: load 4-5g over 1h → 1g/h for 8h or until bleeding controlled - TXA: load 1g over 10min → 1g over 8h cont. infusion - S/E: risk of seizures w/ high dose TXA
Albumin	Types 1. 5% (iso-oncotic) 2. 25% (hyper-oncotic) Both contain 12.5g albumin & 154mEq Na (isotonic)	**5% if hypovol/intravasc depl., 25% if fluid/Na restricted** - Cirrhosis: HRS, SBP, LVP (see *ESLD*) - Shock: 4% albumin similar to 0.9% NS for IVF resuscitation (when alb. >2) (SAFE, NEJM 2004;350:2247) - ARDS: 25% albumin (25g) q8h x3d + lasix gtt x3d → ↑O2, neg. TBB (when alb. <2) (Crit Care 2005;33:1681)	- C/I: traumatic brain injury (Also see *IV Fluids and Electrolyte Repletion*)
IVIG	Types Polyclonal IgG and trace plasma contaminants Dose adjust for obesity	- Immunodeficiency: hypogammaglobulinemia IgG <400 - Immunosuppression in autoimmune disease (e.g. ITP, AIHA, post-transfusion purpura, acquired VWS) - Neuro: CIDP, myasthenia gravis, GBS - ID: toxic shock syndrome, Kawasaki disease	- SE: infusion reactions, aseptic meningitis, hyperosm renal tubular injury, thrombosis

Maggie Selesky

TRANSFUSION MODIFICATIONS

- **Leukoreduction (LR)**: filters leukocytes to (1) ↓HLA sensitization in chronically transfused pts / **heme malignancies**, bone marrow / kidney / heart / lung **transplant candidates** (not liver transplant) (2) ↓CMV risk & (3) ↓febrile non-hemolytic transfusion reaction
- **Irradiation**: prevents proliferation of donor lymphocytes from attacking the recipient (transfusion-associated-GVHD in 1st degree directed donors); indications: **heme malignancy** & BMT to prevent GVHD; not indications: solid tumor, solid organ transplant, HIV
- **Saline-washing**: removes anti-IgA Ab & plasma proteins; indications: severe anaphylaxis to blood products (w/ or w/o IgA def.)

ADMINISTERING BLOOD PRODUCTS

- **Consent**: required for administration of all blood products, discuss type of product, indication, benefits/risks, possible alternatives
- **Ordering**: "Prepare RBC" (or platelets/FFP/cryo) → select number of units to prepare, indication, applicable modifications (see below) and "Transfuse RBC" → select number of units to administer, and rate of admin (usually over 2-4h)
- **Monitoring response**: order post-transfusion CBC to be drawn 15-30min after transfusion (if not actively bleeding)

MASSIVE TRANSFUSION AND EMERGENCY BLOOD MGH POLICY

Call **Blood Bank (x63623)** & physically run down w/ patient sticker and pick-up slip to **Gray/Bigelow 2** to pick up cooler(s)

Emergency Release Blood: 4u of uncrossmatched whole O blood (for men & women >50y). For women <50y, 6u group O pRBCs (Rh-neg), 3u plasma, and one dose of platelets. Only one cooler, sufficient for most bleeding.

Massive Transfusion Protocol: One cooler of 4u whole O blood followed by coolers of 6u O pRBCs, 3u plasma, and 1 dose platelets released q15min until the blood bank is called to stop. MUST have a blood bank sample sent before 3rd cooler or plasma/platelets will NOT be released.

- Activate MTP when anticipate transfusing 50% TBV (~5U pRBC) in 2h OR 100% TBV (~10U pRBC or 5L plasma) in 24h
- Occurs most commonly in trauma, GI bleeding, cardiac surgery, obstetric complications, rupture of major blood vessel
- Access: Ideal = short and stubby: ≤18g PIV, MAC/Cordis. Take off clave (blue cap) and pressure bag blood vs Belmont.
- **No universally accepted ratio**: 1:1-2:1 (1u pRBC:1-2u FFP:1u plt) transfusion protocol is most common. FYI: 1 bag /dose plt ~4-6u plts
  - Goals: Hb >7-10, INR <2 (unless ESLD), PLT >50k, fibrinogen >100-150
  - Cryoprecipitate is ordered separately from MTP guided by fibrinogen or given empirically (1-2 pools Cyro:7-8 pRBC). FYI: 1 pool=5u
  - Excessive FFP a/w ARDS in pts not requiring massive transfusion.
- Correct coagulopathy → IV vit K/PCC, AC reversal agents, platelet dysfunction (ASA, plavix, uremia) → DDAVP 0.3mcg/kg
- Consider IV amicar or IV TXA (especially in obstetric, surgical, or trauma. Not helpful in GIB (HALT-IT). Dosing on previous page)
- **Complications**: hypothermia (cover pt w/ bair hugger, use blood/fluid warmers), hypo-Ca^{2+} (2/2 citrate, administer CaCl2 to target an iCal of 1-3 mM or consider empiric 1-2g per 6 units pRBC), dilutional coagulopathy esp. w/ IVF, metabolic alkalosis (citrate metabolized to bicarb), hyper-K^+, females of reproductive age may need rhogam post resuscitation.

PLATELET REFRACTORINESS: failure to achieve acceptable ↑platelet count following transfusion. Normal $t_{1/2}$ of 3 days

- Alloimmune: **Ab to class I HLA antigens** (e.g. +PRA) or PLT-specific antigens. RFs for HLA alloimmunization: multiple pregnancies, prior transfusions with non-leukoreduced blood products, organ transplants (NEJM 1997;337:1861). Drug-associated ITP (heparin, sulfa, vanc, linezolid, piperacillin, rifampin, thiazide, anti-GpIIb/IIIa)
- Non-alloimmune: **non-HLA Ab-mediated**; 2/3 of cases; Ddx: sepsis/DIC, HIT, TTP, CVVH/bypass/IABP, splenomegaly, liver dz, HSCT, viral infection (HIV/HCV) & drugs (amphotericin)
- **Evaluation**: check plt post-transfusion on 2 occasions and assess plt recovery (15min-1h later) & plt survival (18-24h later)
  - Inadequate plt recovery: corrected count increment <5k on 2 occasions; also usually indicated by plt ↑ <10k x2 → *alloimmune refractoriness* (JCO 2001;19:1519)
  - Normal plt recovery but ↓survival → non-alloimmune refractoriness
- **Alloimmune refractoriness workup**:
  - Consult Blood Transfusion Service **p21829**. Studies will *not* be processed without discussing w/ them first
  - Send Panel Reactive Antibody: HLA class I Ab screen; test for alloreactivity against HLA antigens. Normal is 0%, range 0-100%
  - **If platelets required urgently** (i.e. actively bleeding), notify Blood Bank and ask for send out to Red Cross
- **Management**: with each platelet transfusion, **must** check a post-transfusion CBC w/in 15-60min of completion
  - Compatible platelets (specific HLA-antigen negative) or crossmatch compatible
  - ABO/HLA-matched apheresis single-donor plts from Red Cross. Takes days to process. Each unit has a shelf life ~3 days
  - Consider Amicar if bleeding (contraindicated in thrombotic DIC); correct coagulopathy with DDAVP if e/o uremia

MANAGEMENT OF ANEMIA IN JEHOVAH'S WITNESSES (Am J Hematol 2017;92:1370)

- Discuss management with patients on a **case-by-case basis**; consider using a checklist of blood product types
- **Acceptable products**: hematinics (iron, folate, B12, recombinant human EPO), non-blood volume expanders (NS, LR, hydroxyethyl starches), hemostatic agents (amicar, TXA, DDAVP, albumin-free clotting factors)
- **Acceptable to some**: autotransfusion, HD/apheresis/bypass/ECMO, hemostatic products w/ blood fractions (coag. factors, PCC), plasma-derived products (albumin, cryo, Ig), products potentially containing albumin (rhEPO, vaccines), BM/organ transplantation
- **Unacceptable products**: whole blood, pRBCs, platelets, FFP, cryo, autologous blood transfusion
- Bleeding, preop: consider IV iron + rhEPO to speed up erythropoiesis → rhEPO onset 2-6 days if Fe/folate/B12 replete
- Critically ill: no expert consensus, consider rhEPO 200-300U/kg IV q24h or 250-500U/kg SQ q48h for goal periop Hb >10-12 → can be extrapolated to hemodynamically unstable/bleeding pts

THERAPEUTIC APHERESIS

- **Plasmapheresis (plasma exchange)**: removes plasma, replaces with saline, albumin or plasma (depending on pt. condition)
  Indications: TTP (replace ADAMTS13, NEJM 1991;325:393), hyperviscosity, cryo, Guillain-Barre, CIDP, MG, ANCA, anti-GBM
- **Cytapheresis**: removes abnormal or excessive # blood cells
  Indications: leukapheresis for hyperleukocytosis (goal WBC <100, controversial); RBC exchange for sickle cell patients with acute decompensation (organ failure, acute chest, etc.), severe babesiosis (high grade parasitemia >10, severe hemolysis, or pulm/liver/renal dz); platelet removal for thrombocytosis rarely done (goal plts <1000)

Hematology

Transfusion Reactions

INITIAL EVALUATION: Blood Bank (**x63623**, **p21829**) (Br J Haematol 2023;201;832)

- S/Sx: f/c/rigors, hives/flushing/pruritis, infusion site pain, shock/oliguria, SOB, wheezing, crackles, hypoxia, angioedema, bleeding diathesis, nausea/vomiting

1. STOP transfusion, ABCs, VS q15min, notify blood bank
2. If only urticarial sx or isolated T ≤39C → treat sx, resume once symptoms resolved
3. Initial workup to consider: CBC, BMP, LFTs
   - High suspicion for hemolysis: DAT, Bili, LDH, hapto, crossmatch, UA, smear
   - High suspicion for sepsis: GS/BCx of both pt & blood product
   - High suspicion for TRALI/TACO: JVP, NT-proBNP, ABG, portable CXR

	Acute	Delayed
Immune-mediated	AHTR, FNHTR, Urticaria/hives, Anaphylactic, TRALI, IgA def	DHTR, TA-GVHD, post-tx purpura
Non-immune mediated	Cold toxicity, citrate toxicity, sepsis, TACO	Viral infection

Reaction/Per-Unit Risk	Presentation/Diagnosis	Pathophysiology	Treatment/Prevention
ACUTE TRANSFUSION REACTIONS (<24H)			
Acute Hemolytic (AHTR) 1/76,000-137,000	**Sx**: 15min to 2-4h; fever/chills, nausea, tachycardia, HoTN, back/flank pain, bleeding, DIC **Dx**: +Hb (blood/urine), +DAT, +Bili/LDH, +smear (spherocytes)	- ABO/Kidd incompatibility (preformed Abs) → intravascular hemolysis (IgM), cytokine/complement activation - Rh/Kell/Duffy incompatibility → less severe extravascular hemolysis	**Tx**: IVF (± diuresis) for goal UOP >100cc/hr x24h - Monitoring: HoTN, AKI, DIC, mortality ∝ volume transfused **PPX**: careful crossmatch
Febrile Non-Hemolytic (FNHTR) 1/14 (PLT) 1/200-2,500 (RBC)	**Sx**: 1-4h; low-grade fever, chills/rigors, HA, flushing **Dx**: hemolysis workup negative, also send BCx (results would be negative)	- Donor WBCs produce TNFα, IL1, IL6 - RBC: donor WBCs activated by recipient anti-HLA Abs - PLT: donor WBCs make cytokines before transfusion	**Tx**: APAP ± meperidine **PPX**: leukoreduction, little evidence for pre-medication
Sepsis (Bacterial Contamination) 1/75,000 (PLT)	**Sx**: 15-60min; high fever, rigors, abd sx, HoTN/shock **Dx**: GS/BCx of both pt & bag	- Bacteria >> viruses in donor blood - RBC: Yersinia, PsA (endotox-GNRs) - PLTs: Staph epi (GPCs)	**Tx**: antibiotics, quarantine all other similar products **PPX**: routine screening
Urticaria/Hives 1/33-100	**Sx**: anytime during/after transfusion; localized or diffuse hives & redness **Dx**: no work-up necessary	- IgE-mediated hypersensitivity to donor plasma proteins	**Tx**: pause → diphenhydramine → resume if urticaria resolves **PPX**: washed products, no evidence for pre-medication
Anaphylactic/ Anaphylactoid 1/20,000-50,000	**Sx**: within min; acute HoTN, angioedema, urticaria, wheezing, abd pain **Dx**: clinical; consider IgA def., serial mast cell tryptase	- IgE-mediated hypersensitivity in recipient lacking IgA or haptoglobin - Bradykinin-mediated flushing/HoTN in pt taking ACEi or neg charged filters (e.g. plasma exchange w/ albumin)	**Tx**: ABCs, O2, IVF ± pressors, epi IM Q15min, methylpred 125mg, diphenhydr. 25-50mg **PPX**: washed products
Transfusion-Related Acute Lung Injury (TRALI) 1/12,000 (RBC) 1/38,000 (PLT)	**Sx**: 1-6h; dyspnea ± fever **Dx**: NT-proBNP nl, bilateral CXR infiltrates w/o CHF, noncardiogenic pulm edema (ARDS)	- Pre-transfusion stress activates lung endothelial cells & primes PMNs - Donor anti-HLA Abs/bioactive factors attack primed PMNs of recipient	**Tx**: ABCs, O2, contact blood bank, intubation **PPX**: male donor plasma (fewer anti-HLA, anti-PMN Abs); defer donors w/ prior assoc. TRALI
Transfusion-Assoc. Circulatory Overload (TACO) 1/100 (RBC)	**Sx**: 1-6h; dyspnea **Dx**: elevated NT-proBNP, CXR w/ cardiogenic pulm. edema 2/2 vol. overload	- Infusion rate or volume that cannot be effectively processed by recipient - Highest risk in elderly, HF, CKD, chronic anemias	**Tx**: O2, IV diuretics, ± nitrates, NiPPV **PPX**: slower rate (1cc/kg/hr)
IVIG Transfusion Reactions 5-15% of infusions	- Inflammatory rxn: fever, chills, flushing, headache, myalgias - Anaphylactoid rxn: urticaria, flushing, chest pain, N/V, HTN	- Inflammatory rxn: Ab/Ag interaction i/s/o concurrent infxn - Anaphylactoid rxn: unknown, potentially kinin-mediated, rare	**Tx**: IVF, sx mgmt **PPX**: slow & space out infusions
DELAYED TRANSFUSION REACTIONS (>24H, <28D)			
Delayed Hemolytic (DHTR) 1/2,000	**Sx**: ~3d; fever, anemia, jaundice, flu-like illness, hemoglobinuria **Dx**: +DAT, +DBili/LDH, +smear w/ spherocytes, low haptoglobin	- Anamnestic IgG against previously exposed antigen (Kidd/Duffy/Kell) → extravascular hemolysis	**Tx**: none *NB*: delayed serologic transfusion reaction is the same except w/o hemolysis
TA-GVHD Rare (typically immunosuppressed)	**Sx**: 2-30d; fever, rash, mucositis, diarrhea, hepatitis, pancytopenia	- Donor T cells attack non-HLA matched recipient organs in s/o immunosuppression or 1st degree relative donor	**PPX**: irradiation
Post-Transfusion Purpura (PTP) Rare (women>>>men)	**Sx**: 3-14d; purpura, mucocutaneous bleed **Dx**: PLT <10,000, anti-HPA-1A	- HPA-1A (common in donor PLTs) HPA-1A neg women develop Abs to	**Tx**: 1st line: IVIG | 2nd: PLEX **PPX**: HPA-1A negative PLTs

Hematology

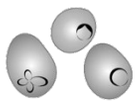
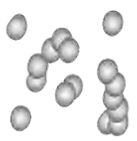
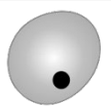
Peripheral Smear Interpretation

General Approach (NEJM 2005;353:498; MGH Slide Rounds)

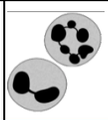
- Special slide: 5th floor Bigelow building, first left off elevators, then another left, proceed down the hall past the Core lab, then second door on your left is the heme lab. Inside heme lab, second enclave on the right has the microscope and special slides next to it.
- Low power (20x): scan slide for WBC distribution. Identify the "thick" edge and the "feathered" or thin edge where RBCs are just apart
- Med power (40x): examine feathered edge for rouleaux, parasites, abnormal WBC, platelet aggregation/microsatellites
- Oil Immersion (100x): assess the size, shape, and morphology of major cell lineages:
  - **RBC**: examine where RBCs are close but not touching. Assess size (compare to a lymphocyte nucleus for scale), morphology (membrane irregularities, fragmentation), color (pallor, reticulocytes)
  - **WBC**: examine at edges and thin end of film. Assess distribution of normal WBC, size, shape, cytoplasm (including granules and vacuolation), and inclusions (such as Dohle bodies). Evaluate neutrophils for nucleus segmenting (average is 3).
  - **Platelet**: assess for appropriate number (1 plt per HPF [high-powered field] = 20K platelets in CBC), giant platelets, granulation

Common Questions Answerable By Peripheral Smear (NEJM 2005;353:498; Harrison's 18th Ed.)

RBC Lineage

Question	Findings	Example	Clinical Significance	Next Steps
Intravascular hemolysis occurring?	Schistocytes (helmet cells, fragments, micro-spherocytes)		>1% schistocytes in HPF + absent alt diagnoses suggests TMA (Int J Lab Hematol 2012;34:107)	- Correlate with CBC, haptoglobin, LDH - Assess for clinical causes of TMA, valve hemolysis. Consider calculating PLASMIC score if concern for TTP
Intra-erythrocytic forms present?	Ring forms in RBCs; less often, tetrad (Babesia)		84% Sn for babesiosis (Ann Rev Pub Health 1998;19:237); 65-74% Sn for malaria (Malar J. 2008;7:22)	- Thick and thin smears for confirmation/parasite burden - Babesia, Lyme, Anaplasma testing
Evidence of iron deficiency?	Hypochromic, microcytic cells; "pencil" cells		>5% hypochromic cells gold standard for functional IDA, incl in pts with active inflammation (Clin Chem 2002;48:1066)	- Iron studies if not yet sent (supplementation if no contraindication) - Consider thalassemia and sickle cell anemia if clinically indicated
Are there rouleaux?	Linear aggregations of RBCs throughout smear (may be artifact at edges)		Associated with Inflammatory, infectious and malignant conditions. Sn but not Sp for MM (Arch Int Med 2002;162:1305). Reflects presence of ⊕ charged proteins, incl. Ig & fibrinogen (Blood 2006;107:4205)	- Correlate for causes of elevated Ig/decreased albumin, incl. infection, inflammation, cirrhosis - Consider quant Ig, SPEP/UPEP. Correlate for CRAB criteria
Functional asplenia?	Howell-Jolly bodies		Sn only for severe splenic hypo-function; inversely prop to functional splenic volume (AJH 2012;87:484)	- Assess for causes of hyposplenia; consider vaccination & antibiotic adjustment accordingly

WBC Lineage

Question	Findings	Example	Clinical Significance	Next Steps
Are PMNs hyper/ hyposegmented?	Hyper: any 6-lobed or >3% w/ 5 lobes. Hypo: 2 lobes		Hyper: 98% Sn megaloblastic anemia, 77% Sp B12 def (Acta Haematol 1989;81:186). Hypo: 92% Sn MDS (Br J Haematol 1986;63:665)	- Check folate/B12, consider supplementation (hyper); MDS workup (hypo)
Are lymphocytes atypical?	Large lymphocytes, extra cytoplasm, prominent nucleoli		≥10% atypical lymphs ⊕LR for infectious mononucleosis (JAMA 2016;35:1502); part of RegiSCAR score for DRESS	- Apply to RegiSCAR; consider EBV/CMV, HIV, Toxoplasma infection

Platelet Lineage

Question	Findings	Clinical Significance	Next Steps
Are giant platelets present?	Large platelets ≥ size of RBC	Suggests marrow response to destruction; incr. plt turnover (ITP); or proliferation (myelo-proliferative dz); clumps suggest pseudo-thrombocytopenia	- Consider peripheral causes of thrombocytopenia incl drug-induced, hemolysis, sequestration - Consider MYH9 and other hereditary plt disorders

Other Common Findings And Implications (Harrison's 18th Ed.)

Target Cells	Acanthocytes (Spur Cells)	Echinocytes (Burr Cells)
Membrane redundancy due to liver disease, thalassemia, HbC disease	Irregular, dense membrane projections present in severe liver disease	Small, uniform membrane projections present in uremia and MAHA

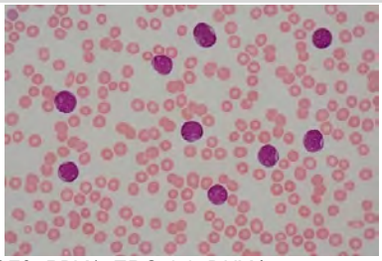
Oncology

Acute Leukemia

General Admission Approach

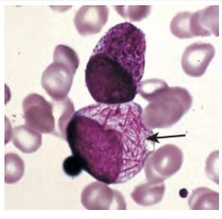
- **History**: sibling status (for donor search), family history (for inherited syndromes), and if pre/peri menopausal, obtain date of LMP
- **Peripheral smear**: anemia, thrombocytopenia, variable WBC, circulating **blasts** ("other cells"), Auer rods (*indicates myeloid origin*)
- **Peripheral flow cytometry**: Collect in yellow top. In Epic, order "Flow cytometry labs (blood)" → fill in Clinical hx; select "Leukemia Panel." To **RUSH case (e.g. for new dx)** send page to *Group 549 - Leukemia Pathology Team* (if not on your directory, call MGH operator and ask for access). Sample is sent to BWH and interpreted by MGH Hemepath. FYI **Routine (non-rush)** are sent to Mayo
- **Screening**: LFTs, lipase, B12, folate, HBV/HCV/HIV serology, CMV IgG, T&S, G6PD, urinalysis, quantitative bHCG (if applicable)
- **Monitoring** (initially q8h): **TLS**: BMP (if ↑WBC, use blood gas K), LDH, uric acid, iCal, Phos, Mg. Cairo-Bishop requires 2 lab (↑uric acid, ↑K, ↑phos, ↓Ca) + 1 clinical (AKI, arrhythmia, seizure); see *Oncologic Emergencies* | **DIC**: PT/INR, PTT, fibrinogen, D-dimer
- **BMBx**: aspirate+core, flow, cytogenetics (+/- FISH), molecular diagnostics (e.g. BWH Rapid Heme Panel, MGH Heme Fusion Assay)
- **Imaging**: **CXR**, **TTE** (prior to induction due to cardiotoxic chemotherapies), **CT head** (if CNS sx)
- **Access**: Coordinate with attending: double-lumen **Hickman** vs. triple-lumen **PICC** if induction anticipated, not needed for venetoclax
- **LP ± intrathecal chemo**: indications for LP → all ALL, AML w/ CNS or ocular symptoms, APL with systemic relapse
  - CT or MRI before LP: AMS, focal neurologic signs, papilledema, seizure within the last week
- **HLA typing**: Initiate allo-HCT work-up if ≤80 yo. In Epic, order "HLA Lab" → select "Specimen Type: Blood," "Patient: Recipient," "Test: Bone Marrow/HSC, Allotransplant – Initial workup." Coordinate w/ RN, as it is difficult to tell if HLA typing is pending in Epic.
- **Use Leukemia Admission Order Set**: Neutropenic precautions | **TLS ppx**: allopurinol 300mg qd (*HLA-B*5801* ↑prevalence in Southeast Asian, black populations, ↑risk of SJS/TEN, consider testing (ACR guidelines) | **GI ppx**: omeprazole 20mg qd | **HSV/VZV ppx**: acyclovir 400mg bid or famciclovir 500mg qd | Hibiclens daily | Peridex mouthwash | **No VTE ppx** (thrombocytopenia)

Acute Lymphoblastic Leukemia (ALL)



- Epi: Bimodal. Peak incidence in children, but another peak in >45yo (68% 5y survival)
- S/Sx: pancytopenia sx (pallor, petechiae/bruises, infections), bone pain, B symptoms, masses (LAD, HSM; anterior mediastinum in T-ALL), CNS sx (CN palsy, n/v, HA), TLS, DIC
- Smear: lymphoblasts with scant cytoplasm, large nuclei containing nucleoli
- Subtypes: B-cell lymphoblastic leukemia/lymphoma (B-ALL/LBL) & T-cell ALL/LBL
  - LBL = lymphoblastic lymphoma → pts w/ extramedullary mass(es) w/ <20% BM blasts
- Risk stratification for AYA and Adults (Lancet 2020;395:1146; Blood 2021;138:948):
  - **B-ALL/LBL** (subtyped by clinical/molecular features):
    - **Favorable**: WBC<30k, <35yrs, hyperdiploidy (>50 chromosomes), *ETV6-RUNX1, TCF3–PBX1, ERG* del, *DUX4*-rearrange
    - **Unfavorable**: ↑WBC, older, CNS/testicular involvement, hypodiploidy (<44 chromosomes), *KMT2A* rearrangement, *BCR-ABL1* (Ph+), *BCR-ABL1*-like (Ph-like, e.g. JAK-STAT pathway abnormalities), *TCF3–HLF*, *MEF2D* rearrangement, ZNF384 rearrangement, iAMP21, *IKZF1* alterations, complex karyotype (≥5 chromosome abnormalities)
  - **T-ALL/LBL**: **Favorable**: *NOTCH1*/*FBXW7* mut. **Unfavorable**: WBC >100k, CNS disease, complex karyotype, *RAS*/*PTEN* mut.
  - **Measurable residual disease (MRD)**: search for leukemic cells using flow cytometry, NGS or RT-PCR of gene fusions. MRD-positivity correlates w/ risk of relapse. MRD evaluation → dynamic risk assessment, therapy decisions (e.g. allo-HCT)
- Treatment (NEJM 2006;354:166; JCO 2011;29:532):
  - *General*: no single best regimen, many (e.g. CALGB 10403, R-Hyper-CVAD, BFM). Incorporate (1) induction (2) consolidation (3) intensification [if needed] (4) CNS therapy [if needed] (5) maintenance (6) allo-HCT [for relapse or unfavorable-risk disease]
    - If pt is AYA (age 15-39), pediatric-inspired regimen often used (usually incorporating asparaginase + ↑corticosteroids)
      - Asparaginase toxicities: hypersensitivity, pancreatitis, hepatotoxicity, thrombosis (Blood 2020;135:987)
    - If *BCR-ABL1*-positive, TKI is used in conjunction w/ chemo (e.g. R-HyperCVAD plus dasatinib) (Blood 2019;133:130)
    - If elderly, low-intensity or chemotherapy-free regimens often used (e.g. dasatinib + blinatumomab, NEJM 2020;383:1613)
  - *CNS ppx*: **intrathecal** MTX/cytarabine vs. **systemic** high-dose MTX w/ leucovorin rescue
  - *Maintenance*: weekly **MTX/6-MP** + monthly **Vinc/Pred** x2-3y (POMP); TKI maintenance if *BCR-ABL1*-positive
  - Relapsed/refractory B-ALL: **blinatumomab** (CD19 BiTE), **inotuzumab ozogamicin** (CD22 ADC), **CAR T-cells**, allo-HCT

Acute Promyelocytic Leukemia (APL)



- Subtype of AML with distinct biology and excellent prognosis (>80% 5y survival) (NEJM 2013;369:111)
- S/Sx: pancytopenia sx (fatigue, anemia, ecchymoses, infection); very high risk for DIC and bleeding
- Smear: **atypical promyelocytes** (large, "dirty" granular, bilobed nuclei), **+Auer rods** (see image to right)
- Cytogenetics: **t(15;17) → *PML-RARα* (>97%)**, rarely t(11;17), t(5;17)
- Treatment (JCO 2017;35:583):
  - **Immediately start ATRA** (all-*trans* retinoic acid) if **any** suspicion for APL given early mortality from coagulopathy and low toxicity. Dose: 45 mg/m^2 in 2 divided doses daily. Target plts >50, fibrinogen >150
- *Induction*: if low-risk (WBC ≤10K): ATRA + arsenic trioxide (ATO)*. If high-risk (WBC >10K): ATRA/ATO + anthracycline or gemtuzumab ozagamicin (CD33 ADC). e. *Consolidation*: ATRA/ATO or gemutzumab ozagamacin. *Monitor qtc
- Complications of ATRA:
  - **Differentiation syndrome**: fever, rising WBC, hypoxemia (pulmonary infilitrates, effusions), peripheral edema, weight gain, AKI → high-dose steroids (dexamethasone 10mg q12h), supportive care, temporary cessation of ATRA if severe.
    - Start primary ppx w/ steroids in highest risk patients (e.g. WBC >10K) (Blood 2014;123:2777).
  - **Hyperleukocytosis**: see *Oncologic Emergencies*
  - **Idiopathic intracranial hypertension**: HA, vision loss, papilledema → hold ATRA, pain control ± steroids/acetazolamide

Dan Ikeda

ACUTE MYELOID LEUKEMIA (AML)

- Pathophysiology: clonal disorder of hematopoietic progenitor cells w/ infiltration of BM, blood, & other tissues. Significant heterogeneity in underlying molecular abnormalities (*see Risk Category table*)
- Epi: most common leukemia in adults (80%). Median age 68 at dx. 5-10% w/ familial syndrome.
- S/Sx: **pancytopenia** (fatigue, petechiae, ecchymoses, infections), myeloid sarcoma, **leukemia cutis** (non-tender red/brown papules/nodules), **neutrophilic dermatosis** (i.e. Sweet syndrome: tender red/violet papules/plaques), gingival hypertrophy (due to leuk. infiltration), joint pain/swelling (leuk. infiltration, gout), **leukostasis** (AML > ALL; typically WBC >50-100K; SOB, HA, blurry vision, stroke), spurious ↑K (check blood gas K); falsely low PaO_2 (check pulse Ox) (see *Oncologic Emergencies*)
- Dx: ≥20% blasts in BM or characteristic translocation (e.g. t(8;21)(q22;q22.1)) or myeloid sarcoma (extramedullary tumor of AML cells). Recent schism in classification (ICC vs. WHO 5th).
- Complications (see *Onc Emergencies*): (1) **DIC →** keep fibrinogen >150, INR <1.5, plt >30-50, add ATRA if any c/f APL [*see APL*] (2) **febrile neutropenia** (3) **TLS →** allopurinol, IVF, rasburicase if uric acid >10 (4) **leukostasis →** hydroxyurea, IVF, leukapheresis, avoid transfusions (can ↑viscosity, worsen). Single dose cytarabine may also be considered if uncontrolled w/ hydroxyurea.
- Subtypes: t-AML (therapy-related from prior chemo, RT), s-AML (secondary from preceding heme disorder, e.g. MDS, MPN, PNH)
- Risk stratification: based on cytogenetics, mutations, performance status (Karnofsky/ECOG), gero assessment (Blood 2013;121:4287)
- Tx: intensive (see below, NEJM 2009;361:1249) vs. non-intensive (**HMA±venetoclax [BCL2 inhibitor]**, NEJM 2020;383:617)
  - Many factors influencing choice: cytogenetics, mutational profiling, performance status (Am J Hematol 2021;96:493)

Risk Category (5y OS)	Genetic Abnormality (NCCN 2024 AML Guidelines)
Favorable (55-65%)	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}
Intermediate (24-41%)	Mutated *NPM1* and *FLT3*-ITD^{high} Wild-type *NPM1* without *FLT3*-ITD or with *FLjkmT3*-ITD^{low} t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Any other cytogenetic abnormalities not favorable or adverse
Poor/ Adverse (5-14%)	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* t(8;16)(p11.2;p13.3)/KAT6A::CREBBP inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2-EVI1* -5 or del(5q); -7; -17/abn(17p) t(3q26.2;v)/MECOM(EVI1)-rearranged Complex karyotype, monosomal karyotype Wild-type *NPM1* and *FLT3*-ITD^{high} Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2 Mutated *TP53*

1) Induction: standard regimen for "medically fit" pts: **"7+3" →**cytarabine (aka "ara-C") continuous infusion days 1-7 + ida/daunorubicin (bolus/short infusion) on days 1-3.
Additional/alternative agents for pts with certain subtypes of AML:
- Midostaurin (TKI) added to 7+3 in AML with *FLT3* mutations (NEJM 2017;377:454)
- Liposomal cytarabine/daunorubicin (Vyxeos): ↑survival in t-AML & s-AML, but longer neutropenia (JCO 2018;36:2684)
- Gemtuzumab ozogamicin added in CD33-positive core-binding factor AML (*RUNX1 or CBFB* translocations, (Blood 2017;130:2373)
- Venetoclax + HMA (azacitidine or decitabine) instead of 7+3 if older and/or adverse risk (e.g. *TP53*). (NEJM 2016;375:2023)

2) Day 14 BM Biopsy: check for residual leukemia

3a) Residual Leukemia: if residual leukemia cells, **re-induction chemo** (e.g. **5+2**) may be given

3b) No Residual Leukemia: if BM is "ablated" (i.e. sufficiently acellular w/o evidence of leukemia), check again for complete remission (CR) at day 28

4) Day 21-25 Count Recovery: await count recovery (may be delayed w/ addition of experimental therapies)

5) Day 28 BM Biopsy: check for CR (<5% blasts in BM, nl CBC); 70-80% if <60 yo; 50-60% if >60 yo

6) Consolidation: initiated soon after firstCR. Goal to eradicate residual disease for sustainedCR. Options include chemo and/or allo-HCT. In general, allo-HCT preferred in poor-risk disease if patient is candidate and has suitable donor. Chemo alone is used in lower-risk disease or if not allo-HCT candidate.
Risk stratification determines management (see table above) (Blood 2017;129:424):
- Favorable risk: **HiDAC (high dose ara-C)** x3-4 cycles
- Intermediate risk: chemo (HiDAC) vs. allo-HCT
- Poor/adverse risk: **allo-HCT** vs. clinical trial

7) Surveillance: CBC q1-3mo for 2y, then q3-6mo up to 5y

8) Survivorship: cardiac, psychosocial, vaccines, etc.

Salvage : If residual disease on surveillance (relapsed) or persistent disease after induction (refractory), initiate salvage therapy with goal of inducing complete remission and bridging to allo-HCT or clinical trial (Blood 2024;143:11).. ***IDH1* mutated →** Ivosidenib (NEJM 386(16):1519) or Olutasidenib (Blood Adv 2023;7:3117) | ***IDH2* mutated →** Enasidenib (Blood 2017;130(6):722) | ***FLT3* mutated →** Gilteritinib (NEJM 2019; 381:1728) | **Chemotherapy →** 7+3 (esp. if earlier durable response), HiDAC, mitoxantrone + etoposide + araC (MEC), fludarabine + araC + G-CSF + idarubicin (FLAG-Ida), others | **HMA ± venetoclax**

Dan Ikeda

Oncology Lymphadenopathy & Lymphoma

Evaluation of Lymphadenopathy (AFP 2016;94:896)

- Generalized LAD: HIV, EBV/CMV/toxo, mycobacteria, SLE, meds (e.g. phenytoin), sarcoid, lymphoma, Castleman's, Kikuchi dz, IgG4
- Localized LAD: cervical (EBV/CMV/toxo, mycobacteria, lymphoma), supraclav. (malignancy), axillary (infection, breast), inguinal (STI)
- Hx: chronicity, exposures, travel, meds, B symptoms (fever, night sweats, >10% unintentional wt loss in 6mo), infxn/malignancy ROS
- Exam: localization (think about area of nodal drainage), size (abnormal >1cm), consistency, fixation, tenderness (inflammation)
- Labs: CBC/diff, LDH, HIV (PCR if acute), HBV, HCV. Depending on pre-test probability: T-spot, RPR, ANA, EBV/CMV/toxo serologies
- Imaging: CT C/A/P w/ contrast, PET/CT can define node size, distribution, monitoring of response/progression (w/ Deauville scoring)
- Biopsy: consider if large (>2cm), persistent 4-6w, or increased size, w/ immunophenotyping & cytogenetics. Empiric steroids may decrease yield of biopsy. **Excisional** (cells & nodal architecture) > core needle (tissue for molecular studies) > FNA (high false neg.)

Lymphoma General Principles

Lymphoma Staging: if Hodgkin lymphoma (HL), add "B" if B Sx. PET Deauville score (1-5): 1 = no FDG uptake; 5 = markedly FDG-avid

Stage I: 1 LN region, or single extralymphatic organ Stage III: LN groups above and below diaphragm

Stage II: ≥2 LN groups on same side of diaphragm Stage IV: disseminated ≥1 extralymphatic organs

LN region: cervical (R/L), axillary (R/L), subpectoral (R/L), mediastinal, hilar (R/L), celiac, paraaortic, mesenteric, iliac (R/L), inguinal (R/L)

Workup: PET/CT, HBV/HCV/HIV serology, G6PD, quantitative bHCG (if applicable), PFTs (+DLCO), TTE (prior to anticipated chemo)

Fertility Preservation: sperm/oocyte/ovarian tissue cryopreservation prior to tx. Menstrual suppression: GnRH agonists if ↓plt expected

Hodgkin Lymphoma (NCCN; 2024)

Bimodal age distribution (Lancet 2012;380:836). Reed-Sternberg cells (**CD15+ CD30+** CD20- CD45- PAX5+ PD-L1+) in inflammatory milieu

S/Sx: neck LAD, mediastinal mass, pruritis, constitutional sx, ↑Eos. Rare: burning pain w/ alcohol, nephrotic syndrome (i.e. minimal change disease), liver dysfunction, skin lesions

WHO classification: nodular sclerosis (70%), mixed cellularity (25%), lymphocyte rich (5%), lymphocyte depleted (<1%). Nodular lymphocyte-predominant HL is distinct entity.

Treatment: note long-term risk of cardio- and pulm-toxicity, 2° malignancy (t-AML)

- **Stage I-II**: ABVD ± XRT. **Stage III-IV**: ABVD vs. BV-AVD (NEJM 2018;378:331) vs. BEACOPP ± XRT. Interim PET/CT for escalating vs. de-escalating tx
- **Relapsed/refractory**: salvage chemo (ICE vs GVD) + auto-HCT; brentuximab vedotin (BV); PD1 inhibition (pembro or nivo), bendamustine, allo-HCT

HL International Prognostic Score (IPS)
1 point/factor (JCO 2012;30:3383)

	Points	5y PFS
Age >45	0	88%
Male	1	84%
Stage IV	2	80%
Albumin <4	3	74%
Hb <10.5	4	67%
WBC ≥15,000	≥5	62%
Lymphocytes <600 <8%		

Non-Hodgkin Lymphoma

Most common blood cancer, a/w immunosupp., autoimmunity, infection (EBV, H. pylori, HCV, HIV, HHV8, HTLV1) (Lancet 2012;380:848)

Indolent (e.g. FL): incurable, but better prognosis (monitor for transformation) vs. **Aggressive (e.g. DLBCL)**: curable, but worse prognosis

Diagnosis	% of NHL	Clinical Features	Treatment
Diffuse Large B-cell (DLBCL)	~35%	Aggressive, rapid growth, nodal/extranodal *BCL2*, *BCL6*, or *MYC* translocations common Prognosis: **IPI**, cell-of-origin (GCB > ABC) **Double-hit lymphoma (DHL)**: more aggressive subtype w/ *MYC* + either *BCL2* or *BCL6* translocations. Triple-hit = ultra-HR.	- Stage I-II: R-CHOP + RT; Stage III-IV: R-CHOP; if DHL, consider more aggressive Tx (i.e. R-EPOCH); if old/frail, R-mini-CHOP - IT MTX CNS ppx for high CNS-IPI **controversial** (JCO 2023;41:35) - Relapsed/refractory: CD19 CAR T-cells preferred (Lancet 2022;399:2294, NEJM 2022;386:640) vs. chemo + auto-HCT vs Ab-drug conjugates (using polatuzumab) (NEJM 2022;386:351)
Follicular (FL)	~25%	Generally indolent; occasionally aggressive **t(14:18) BCL2+.** High grade = more centroblasts. **FLIPI** score prognostic	- Stage I/contiguous II: Observe; RT preferred; Stage II-IV: observation, anti-CD20 ± bendamustine (BR), lenalidomide (LR), CHOP, or CVP; R/R: CAR-T, PI3K inhibitors (JNCCN 2023;21-11) - Monitor for transformation (rapid LN growth, ↑LDH, B symptoms)
T-cell lymphoma	~15%	Diverse varieties. Peripheral T-cell (**PTCL**) NOS most common. Cutaneous T-cell (**CTCL**) i.e. Mycosis fungoides, Sezary syndrome (disseminated). Anaplastic large cell (**ALCL**) a/w *ALK*, breast implants. Adult T-cell leukemia/ lymphoma (**ATL**) a/w HTLV-1, geography (e.g. Caribbean). Enteropathy-associated T-cell (**EATL**) a/w celiac disease	
Marginal Zone (MZL)	~10%	**Extranodal MZL (MALT)**: a/w sites with chronic inflammation, e.g. stomach w/ **H. pylori+ t(11;18)**, salivary glands (Sjogren's), thyroid (Hashimoto's), small intestine, etc. **Splenic MZL**: often HCV+, cryoglobulinemia **Nodal MZL**: generally indolent, similar to FL	- Gastric MALT: if H. Pylori+, quad Tx can cure; if H. Pylori-, RT - Nongastric extranodal localized: RT, observation - Advanced nodal: observe, rituximab + chlorambucil/bendamustine - Splenic MZL: if HCV+, HCV Tx can lead to regression. If HCV-, Rituxumab (preferred) or splenectomy (definitive for diagnosis to differentiate from splenic diffuse red pulp small B-cell lymphoma)
Small or chronic lymphocytic (SLL/CLL)	~5%	Often indolent, painless LAD, **IgM M-protein** No risk of leukostasis unless WBC >400k Prognosis: **Rai**/**Binet**, IGHV unmutated (HR), ZAP70+ (HR), CD38+ (HR), FISH (del17p = HR), genetics (*TP53* mut. = HR)	- Only treat when "active" (Blood 2018;131:2745), i.e. cytopenia, bulky disease, progressive lymphocytosis w/ increase >50% over 2mo, autoimmune dz (AIHA, ITP), significant constitutional symptoms - Evolving combinations with BTKi (zanubrutinib, acalabrutinib, ibrutinib), anti-CD20 (obinituzumab, rituximab), and venetoclax
Mantle Cell (MCL)	~5%	Wide clinical spectrum, can involve spleen, GI, BM. Leukemic (SOX11-) often indolent **t(11;14),** cyclin D1+. MIPI score prognostic	- Stage I/non-bulk II: BR, VR-CAP, R-CHOP, or LR + R maintenance - Stage II-IV: RDHAP ± R-CHOP, NORDIC, or R-B ± R-HiDAc + BTKi vs auto-HCT w/ R maint (Blood 2022;140:1). R/R: BTKi, CAR T
Burkitt (BL)	~1%	Aggressive, extranodal sites (jaw if African). ↑spont. TLS. **t(8:14), cMYC+**, EBV/HIV	- More aggressive than DLBCL treatment: R-EPOCH, R-CODOX-M/IVAC, R-HyperCVAD. Relapsed: chemo + auto- or allo-HCT

ABVD = Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
BEACOPP = Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone
CHOP = Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CODOX-M/IVAC = Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Ifosfamide, Etoposide, Cytarabine
CVP = Cyclophosphamide, Vincristine, Prednisolone
DHAP= Rituximab, Dex, Cytarabine and Carbo-, -Cis- or Oxali-platin
EPOCH = Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
HyperCVAD = Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, alternated w/ methotrexate & cytarabine, followed by maintenance POMP
R-B ± R-HiDAc = Rituxmiab/Bendamustine x3 + Rituximab/High-Dose Cytarabine x3
VR-CAP = Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone

Evaluation of Plasma Cell Disorders (Leukemia 2009;23:215)

Evaluation	Utility	When to Send
Ig Levels	**Quantify** immunoglobulin (Ig) levels in blood (IgG, IgM, IgA, IgD, IgE). Will not discern monoclonal vs. polyclonal	If suspecting a 1° (e.g. B cell deficiency) or 2° humoral immunodeficiency *Consider repleting w/ IVIg if IgG < 400 mg/dL*
SPEP	**Detect/quantify** M-protein (monoclonal protein = M-spike = paraprotein), Ig from an abnormally expanded B/plasma cell	If suspecting a monoclonal B-cell or plasma cell disorder, **send SPEP & FLC**. FLC ↑sensitivity. "SPEP panel" order contains quantitative IgG/A/M, total protein, SPEP & reflex IF. **Serum FLC is separate order**. *At MGH lab, cannot force SIFE if no M-spike on SPEP (FLC assay should be sufficient in most of these cases)*
Serum IF	**Identify** the type of M-protein (intact Ig [G, M, A, D, E], light chain only [LC: κ or λ], or heavy chain only)*	
Serum FLC Assay	**Identify** light chain abundance (outside normal κ/λ ratio 0.26-1.65) Normal ratio w/ ↓LC = immunosuppression Normal ratio w/ ↑LC = infection/inflammation or ↓renal clearance**	
UPEP	**Detect/quantify** Bence Jones Protein (BJP, i.e. urine monoclonal protein, which is typically κ or λ LC). UA/dipstick will miss BJP	**Not** needed unless high suspicion (+M-prot/abnl FLC). If UPEP+, can use 24h UProt to quantify
Urine IF	**Identify** the type of BJP (κ or λ)	If UPEP+ for BJP (reflex)

*Some therapeutic antibodies may show up in above assays as false positives (e.g. daratumumab)
** LC clearance in CKD: eGFR ≥60, κ/λ 0.26-1.65 | eGFR 45-59, κ/λ 0.46–2.62 | eGFR 30-44, κ/λ 0.48–3.38 | eGFR <30, κ/λ 0.54–3.30 (BCJ 2022;12:133)

Classifying Plasma Cell Disorders (Lancet Oncol 2014;15:e358)

CRAB criteria: **C**a^{++} (>11mg/dL), **R**enal dz (Cr >2), **A**nemia (Hgb <10), **B**one lesions (≥1 focal lytic lesion on whole body-CT, MRI or PET)
All those with **M-protein** ≥1.5g/dL, **Non-IgG M-protein** of any size, **abnormal FLC** assay, or **CRAB** should have **BM biopsy** to work-up

	MGUS	Smoldering MM	Multiple Myeloma (MM)	Waldenström (WM)	AL Amyloid
BM Involvement (%)	<10	10-60	≥10 (or plasmacytoma)	≥10	<10
Serum M-protein (g/dL)	<3	≥3	Present	Present (IgM)	<3
Clinical Signs	Absent	Absent	CRAB, *unless SLiM**	Hyperviscosity, etc. (see below)	Present

- **Approach to abnormal asymptomatic SPEP (IMWG)**:
  - If M prot > 3g/dL, classified as **SMM**:. If 1-2/3, **Intermediate-Risk MGUS;** If 0/3, **Low-Risk MGUS**
    - Risk Factors: (1) ≥1.5 g/dL (2) non-IgG (3) +/- abnl. FLC ratio
  - If **SMM**: Refer to Medical Oncology
  - If **Intermediate-Risk MGUS**: Refer to Onc. If SPEP/SFLC stable in 6mo, repeat annually, consider stopping if ↓functional status.
  - If **Low-Risk MGUS**: Repeat SPEP/SFLC in 6mo, if stable Q2-3Y or if CRAB crit develop, consider stopping if ↓functional status.
- **Smoldering MM (SMM)**: prog. to MM 10%/yr for 5yr, then ↓. "20-2-20" risk strat (BCJ 2018;8:59). Tx: controversial (JCO 2020;38:112)
- **MM**: ≥10% BM clonal PC & CRAB symptoms. *If ≥60% BM PC *or* involved/uninvolved FLC ratio ≥100 *or* >1 bone lesion on MRI (w/ <10% BM PC) → MM dx w/o CRAB ("SLiM"). Rarer MM types: ~20% LC-only; ~5-10% oligo-secretory (low M-protein); ~3% non-sec.
- **Solitary Plasmacytoma**: single biopsy-proven tumor w/ clonal PC, imaging w/o other lytic lesions, no CRAB. Tx: RT, monitor for MM
- **WM**: lymphoplasmacytic lymphoma in BM/LN + IgM M-protein. S/Sx: LAD/HSM, anemia, hyperviscosity (HA, vertigo, dizzy, Δ vision, AMS), bleeding (acq VWD), cryoglobulins, cold agglutinins. Measure viscosity. Tx: bendamustine+α-CD-20, BTKi, plasmapheresis
- **AL amyloid**: S/Sx: cardiomyopathy, purpura, nephrotic sx, polyneuropathy, orthostasis, HSM, macroglossia. Congo-red stain (apple-green birefringence) on affected organ or fat-pad. Send for mass spec. Tx: Daratumumab-CyBorD, early auto-HCT if candidate
- **Monoclonal Gammopathy of Renal Significance (MGRS)**: collection of disorders leading to kidney disease, including light chain & heavy chain deposition disease, proliferative GN w/ monoclonal immunoglobulin deposits, C3 glomerulopathy (NEJM 2021;384:1931)
- **POEMS syndrome**: (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes),↑VEGF, sclerotic bone lesions, & Castleman disease. ~λ only. Polyneuropathy & MGUS required for dx. Endocrinopathy: hypo-gonad, -thyroid, -adrenal, etc. Tx: ~MM
- **Other**: Cryoglobulinemia, CANOMAD, DADS-M, Scleromyxedema, Schnitzler's, Clarkson's (cap. leak), TEMPI (ASH 2020:2020;380)

Multiple Myeloma Workup and Management (Nat Rev Dis Primers 2017;3:17046; NCCN 2024 MM Guidelines)

- **Lab findings/workup**: ↓AG ratio, ↑globulin, ↑ESR, peripheral smear (rouleaux), ↑LDH, ↑β2M, SPEP/IFE/FLC, whole body low-dose CT ± PET or MRI. BMBx (IHC, flow, cytogenetics/FISH, rapid heme panel). 10% w/ concurrent amyloid. 10-30% w/ extramedullary dz
- **Risk stratification**: by age, performance status, comorbidities, R-ISS staging (incorporates cytogenetics/FISH, LDH, β2M, albumin). High-risk features: t(4;14), t(14;16), t(14;20), amp1q, del17p, extramedullary dz, circulating PC. **≥2 HR FISH** = "double-hit" (ultra-HR)
- **Treatment agents**: most common induction regimens combine a proteasome inhibitor, immunomodulator, & steroids/chemo:
  - Proteasome inhibitors: bortezomib (Velcade – V, Bor), carfilzomib (K), ixazomib (Ix)
  - Immunomodulatory agents (IMiDs): lenalidomide (Revlimid – R), pomalidomide (Pom), thalidomide (T), iberdomide
  - Steroids/chemo: dexamethasone (low dose = d), prednisone (P), melphalan (M), cyclophosphamide (Cy), doxorubicin (dox)
  - Monoclonal Abs: anti-CD38 daratumumab (D, Dara; NEJM 2019;380:2104) & isatuximab (Isa); anti-SLAMF7 elotuzumab (Elo)
- **Induction & consolidation**: NOT curative. Standard risk median OS approaching 10y. High risk median OS ~3y
  - Induction: triple w/ VRd most common; CyBorD if renal failure at diagnosis; DaraRd if frail; quad (DaraVRd) ↑use, esp. if HR
  - If candidate for autoHCT, usually performed early, but can delay until relapse w/o detriment in OS (NEJM 2017;376:1311)
  - Maintenance (e.g. **R** +/- **V**) following auto-HCT, or after induction if no HCT. A/w ↑OS (JCO 2017;35:3279), but ↑2° cancers
- **Response criteria**: ↑depth a/w better outcomes: partial resp. (↓M-protein 50-90%); very good partial resp. (↓M-protein >90%); complete response (no M-protein, <5% BM PC); measurable residual disease-negative (<1 PC in 10^5 cells on flow/VDJ sequencing)
- **Relapsed/refractory MM**: CAR-T (BCMA, GPRC5D), BiTE (teclistamab, elranatamab, talquetamab), venetoclax if t(11;14), chemo
- Other Tx: aimed at reducing skeletal lesions/fractures (bisphosphonates, denosumab, XRT), hyperCa^{++}, renal damage, hyperviscosity, infections (PCP, HSV, fungal, VZV; depending on Tx), VTE (aspirin vs. AC for IMiD-induced thrombotic risk), anemia (EPO-analog)

MYELODYSPLASTIC NEOPLASMS/SYNDROMES (MPN/MDS)

- Pathophys: clonal mutation → ineffective/dysmorphic hematopoiesis → cytopenias, risk of transf. to AML, and reduced survival
- Presentation: median age 65-75; s/sx include fatigue (55%), fever/infection (15%), and bleeding (8%)
- RF: old age, male, exposures (benzene, tobacco, chemotherapy, XRT), autoimmune disorders (rheumatic heart dz, RA), PNH
- Diagnosis: 1+ cytopenia, BMBx with dysplasia >10% of cells in at least one lineage and <20% blasts, cytogenetics
  - Initial eval: CBC/diff, blood smear, BMBx w/ aspirate, EPO, broad work-up to rule out other causes of bone marrow failure and peripheral cytopenias (nutritional, infectious, autoimmune, endocrine, drug-related)
  - Classification systems (WHO vs ICC) categorize MDS subtypes according to genetic changes, degree of dysplasia & BM blast %
- Prognosis: IPSS-M > IPSS-R predicts progression to AML and survival, which ranges from < 1yr in "very high" risk to 8-10 yrs in "very low" risk. *TP53* multi-hit (not monoallelic), *FLT3*, *KMT2A* partial tandem duplication, and other mutations confer risk.
- Treatment: based on IPSS-R, performance status & age
  - *Low risk:* No intervention shown to improve survival (JAMA 2022;328:872). Supportive care if asx or mild cytopenias. ESA for anemia, TPO-RA for thrombocytopenia. Hypomethylating agents (azacitidine/decitabine) or ATG if multiple cytopenias. alloHCT in select, younger pts. Targeted tx: lenalidomide for del(5q), luspatercept for ringed sideroblastic (NEJM 2020;382:140).
  - *High risk*: If alloHCT candidate, transplant +/- induction or hypomethylating prior (alloHCT improves outcomes even up to age 75, per JCO 2021;39:3328). If not alloHCT, azacitidine or decitabine. Ongoing trials with venetoclax plus azacitidine.

Clonal hematopoiesis (CH) is increasingly identified in patients without frank myeloid malignancy; categories of CH include:

- **Clonal Hematopoiesis of Undetermined Potential (CHIP)**: risk factor for MDS/AML and cardiovascular disease, variant allele frequency (VAF) ≥2% of leukemia-associated gene, no cytopenias, <5% BM blasts, rate of progression to AML 0.5-1%/yr
- **Clonal Cytopenia of Unknown Significance (CCUS):** unexplained cytopenia + CHIP
- **Idiopathic Cytopenia of Unknown Significance (ICUS)**: unexplained cytopenia, but not CHIP (either VAF <2% or no mutation)

MYELOPROLIFERATIVE NEOPLASMS (MPN): clonal expansion, 1+ myeloid lineages, often involve activation of JAK-STAT

Sequelae vary; PV/ET can progress to 2° MF (~10-20%) or straight to AML (<5%). MF progression to AML is more common (10-20%).
Tx goals: improve quality of life (e.g. constitutional symptoms, splenomegaly w/ JAKi), prevent thrombosis (aspirin), prevent progression to AML (alloHCT)

	Polycythemia vera (↑Hgb +/-↑WBC ↑Plt)	Essential thrombocythemia (↑Plt)	Primary myelofibrosis (↓Hgb ↓or↑WBC ↓or↑Plt)	Chronic myeloid leukemia (↓Hgb ↑WBC ↑Plt)
Sx	VTE, aquagenic pruritus, erythromelalgia, splenomegaly, ruddy complexion, GI (epigastric pain, ulcers), HA, dizziness, Δ vision, gout flare	Thrombosis, bleeding (acquired vWF, consider if plt >1 mil), vasomotor sx (HA, syncope, Δ vision, CP, paresthesia erythromelalgia, livido)	Fatigue, night sweats, weight loss, bone pain, massive hepatosplenomegaly, abdominal pain, early satiety, thrombotic/hemorrhagic events	Fatigue, weight loss, night sweats, bleeding, splenomegaly, abdominal pain (LUQ), L shoulder pain (Kehr's sign), gout flare. 20-50% are asymptomatic at diagnosis
Dx	**Major WHO criteria**: - Hgb >16.5 (♂), Hgb >16 (♀) - BMBx showing trilineage proliferation - Mutations: *JAK2* V617F (95-97%) or *JAK2* exon 12 mut. **Minor WHO criteria**: - Low Epo (below reference)	**Major WHO criteria**: - Plt >450k - BMBx w/ enlarged megakaryocytes with hyperlobulated nuclei Mutations: *JAK2* 60-65%, *CALR* 20-25%, *MPL* 5% **Minor WHO criteria**: - Other clonal markers	**Major WHO criteria**: - BMBx w/ "dry" tap showing reticulin or collagen fibrosis - Mutations: *JAK2* 65%, *CALR* 25%, *MPL* 5%, others **Minor WHO criteria**: - Leukoerythroblastic smear (left-shift, nucleated and teardrop RBCs), ↑LDH, anemia, splenomegaly	**Mutation**: ***BCR-ABL1* fusion** (by FISH, RT-PCR), CBC with ↑ granulocytes (myelo, metamyelo, bands), basophilia, eos. Phases: **chronic**, **accelerated** (10-20% blasts), or **blast** (>20% blasts). Blast phase can be consistent with AML (80%) or ALL (20%)
Tx	**All**: phlebotomy (goal HCT < 45), ASA81 (if no bleeding), allopurinol, antihistamine **If >60, ↑risk thrombosis**: Hydroxyurea (HU) or IFN-α, **2nd line**: ruxolitinib (JAK2-inhib, NEJM 2015;372:426)	**All**: ASA81 (unless vWF syndrome). **If age>60 or ↑risk thrombosis**: HU > interferon-α > anagrelide (PDE inhib, blocks plt production) (NEJM 2005;353:33)	AlloHCT (only cure), transfusion, hydroxyurea, ruxolitinib (JAK2 inhibitor, primary benefit is symptom reduction, splenomegaly) (NEJM 2012;366:787). Momelotibin/fedratinib for relapsed/refractory.	**Chronic phase:** TKI: imatinib, dasatinib, nilotinib. 2nd gen TKI (ponatinib > asciminib) if T315I mutation. Consider alloHCT if TKI intolerant, resistance. **Blast phase:** Tx as AML/ALL w/ induction + TKI, alloHCT
DDx	↑**Epo**: hypoxia-induced (heart/lung dz, carboxy-Hb, smoking) vs. Epo-producing tumor (rare). ↓Epo: activating epo receptor mutation (rare)	Infection, inflammation, iron deficiency, splenectomy, bleeding, other MPN (PMF), MDS (e.g. 5q-), solid cancers	AML, CML, ET, PV, MDS/MPN overlap syndromes, MDS, hairy cell leukemia, other malignancies (e.g. w/ bone metastases)	Leukemoid rxn (↑LAP), drugs (steroids, GCSF, ATRA), infection (C. diff, mono), bleeding, splenectomy, DKA, organ necrosis, other MPN

OTHER MYELOID DISORDERS: WHO 2022 classification. Variety of conditions ranging from aggressive to indolent

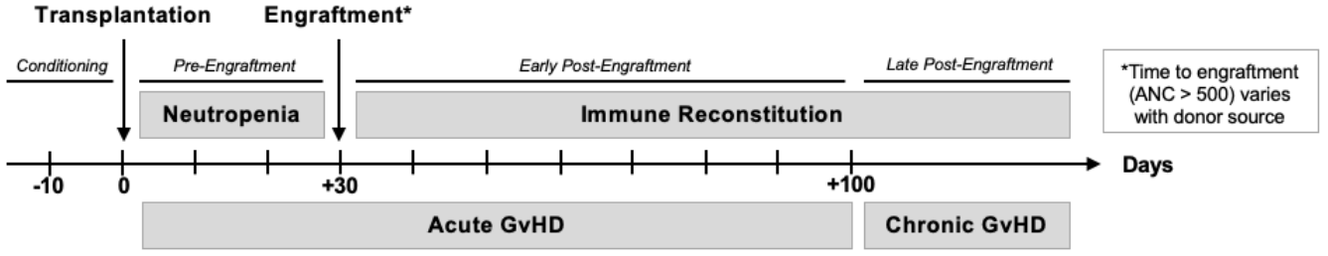
- **MDS/MPN syndromes:** Chronic myelomonocytic leukemia (CMML; see below); MDS/MPN with SF3B1 mutation/ring sideroblasts & thrombocytosis; MDS/MPN with neutrophilia ("atypical CML")
  - **CMML:** characterized by peripheral blood monocytosis (≥1x10⁹/L or ≥10%) and MDS/MPN features. Proliferative (WBC ≥13k) vs. dysplastic (<13k). Prognosis: Mayo Molecular. ↑Prog. to AML. Tx: supportive, HU, alloHCT
- **Blastic plasmacytoid dendritic cell neoplasm (BPDCN):** skin lesions, w/ or w/o marrow involvement and leukemic dissemination
- **Mastocytosis**: includes cutaneous and systemic mastocytosis. Associated w/ *KIT* D816V. +Darier's sign. Recurrent anaphylaxis

Oncology Hematopoietic Stem Cell Transplantation

TYPES OF TRANSPLANT

	Allogeneic Transplant	Autologous Transplant
Definition	Transplant of **non-self (donor)** hematopoietic cells	Transplant of **self (patient)** hematopoietic cells
Goals	**Reconstitute hematopoiesis** after conditioning chemo and **graft-versus-tumor (GVT) effect** to kill malignant cells. Also used for bone marrow failure syndromes. Always curative intent.	**Reconstitute hematopoiesis after high-dose chemotherapy**. Intent generally curative except in plasma cell disorders, where goal is to prolong remission
Indications	↑risk **AML** (40-60% 5YS), **ALL** (40-50% 5YS), **MDS** (45% 5YS), ↑risk **myelofibrosis**, TKI-resistant **CML**, **relapsed lymphoma**, **aplastic anemia,** thalassemia, sickle cell disease, primary immunodeficiency (SCID), inborn errors of metabolism	**1st relapsed lymphomas** (40-50% 5YS), **MM** (35% 5YS); relapsed **Waldenström**, **AL amyloidosis**, select solid tumors (germ cell, neuroblastoma, Ewing sarcoma), autoimmune disease (MS, SS, Crohns, SLE)
Source of cells	Mostly **peripheral blood**, but some centers use more **bone marrow** given lower risk of chronic GVH. Umbilical cord blood is occasionally used	Usually **peripheral blood** given less invasive harvest, more rapid engraftment
Time to engraftment	14-28 days (time for CB > BM > PBSC)	10-14 days
Graft-versus-host disease (GVHD)	**Yes**, skin, liver, GI most commonly affected ***Acute*** (within 100 days) ***Chronic*** (>100d, morbidity/mortality mo/yrs later)	**No**, but rare "GVHD-like" syndrome occurs in ~0.5% of auto-transplants (BMT 2020;55:1879)
Graft-versus-tumor (GVT)	**Yes**, major therapeutic goal is for donor T cells to engraft and attack host tumor cells	**Likely no**, but mechanism via CD8+ T cells under investigation (JCI 2019;129:48)
Pharmacologic Immunosupression	**Yes** (usually 3-6 months; sometimes for 1-2y if GVHD develops)	**No**

ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT (NEJM 2006;354:1813)



- **Donor types**: matched to pt by HLA typing to **minimize GVHD**; matching at alleles **A, B, C, DR, DQ**
  - **Matched-related donor (MRD)**: compatible siblings, matched at 10/10 HLA alleles
  - **Matched-unrelated donor (MUD)**: NMDP database, matched at 8-9/10 HLA alleles
  - **Haploidentical**: any parent/sib/child (~universal), match at 5/10 HLA alleles, ↑GVT via NK cells (Front Immun 2020;11:191)

Cell Source	Collection	Engraft	GVHD Risk	Notes
Bone marrow (BM)	Aspirated from iliac crest	18-21d	(Reference)	Less often used despite lower cGVHD risk, due to slower/less effective engraftment
Peripheral blood (PBSC)	Mobilization and peripheral apheresis	12-15d	Higher risk	Generally preferred source due to faster engraftment (Cochrane Rev 2014)
Cord blood (CB) (Blood 2013;122:491)	Immature cells from umbilical cord at delivery	28d (variable)	Lower risk	↑txp-mortality compared to MUD (similar DFS/OS); allows for more HLA disparity

- **Conditioning regimens** (Blood 2014;124:344): determined by underlying condition, disease status, and performance status
  - **Myeloablative conditioning**: complete disease eradication & ablation of host BM/immune cells
    - Used for young healthy patients, in remission or with measurable residual disease (MRD) (JCO 2020;38:1273)
      ↑toxicity, ↑immunosuppr, ↑txp-mortality, ↓relapse
  - **Reduced intensity conditioning** (**RIC**): tumor debulking & allows for engraftment
    - Permits transplant in elderly w/ co-morbidities; ↓toxicity, ↓txp-mortality, ↑relapse (JCO 2017;35:1154)
  - Conditioning agents: chemo (ex. alkylating agents – fludarabine, busulfan, cyclophos., melphalan) ± total body irradiation

TERMINOLOGY

- One-liners include: underlying diagnosis; **autologous** vs **allogeneic** transplant; **day since transplant** (transplant = d0, day before = d-1, day after = d+1); **conditioning regimen** (myeloablative vs RIC/non-myeloablative); **donor type** (MRD, MUD, haploidentical), **cell source** (BM, PB, CB), **GVHD prophylaxis** regimen (tac vs. cyclosporine, methotrexate, etc.)
- Example one-liner: 35M w/ AML (FLT3-mutated) who is now day +4 from his **myeloablative** (Bu/Cy) matched related donor (**MRD**) peripheral blood hematopoietic-cell transplant (**PBHCT**) with tacrolimus/methotrexate GVHD prophylaxis (day 0 = 1/1/21).

Oncology Hematopoietic Stem Cell Transplantation

INFECTIOUS COMPLICATIONS: 2/2 chemo-related pancytopenia & immunosuppression (ASBMT/IDSA: BBMT 2009;15:1143)

MGH Ellucid	Day 0-30 Pre-Engraftment	Day 30-100 Early Post-Engraftment	Day 100+ Late Post-Engraftment
Immune Defect	Neutropenic, mucositis, lines, acute GVHD	Poor cellular immunity, acute GVHD	Poor cellular and humoral immunity, chronic GVHD
Bacterial	GPCs & **GNRs** (F&N) Neutropenic enterocolitis (**typhlitis**)	GPCs & GNRs	**Encapsulated bacteria** (SHiN) Nocardia
Viral	Resp/enteral (adeno, flu, RSV, paraflu), HSV	Resp/enteral (adeno, flu, RSV, paraflu), EBV (risk of PTLD), CMV, HHV6 (screen for in CB tx)	Resp/enteral (adeno, flu, RSV, paraflu), EBV (PTLD), VZV, BK (hemorrhagic cystitis), **JC** (PML)
Fungal	Aspergillus, candida	Aspergillus, candida, **PJP**	**Aspergillus, PJP**
Parasitic	-	**Toxo**	Toxo (can mimic PJP PNA)

- **Neutropenic enterocolitis** (**typhlitis**): polymicrobial infxn leading to necrotizing enterocolitis, most often involving cecum
  - S/Sx: fever, ANC <500, abdominal pain (often RLQ), n/v, watery/bloody diarrhea
  - Micro: polymicrobial (GPC/GNR/anaerobes/fungal), clostridium septicum a/w fulminant course & high mortality rate
  - Dx: CT (I+/O+) w/ bowel wall thickening, mesenteric stranding, bowel dilatation, mucosal enhancement, pneumatosis
  - Tx: pip/tazo vs -penem vs cefepime/MNZ + ***surgery c/s*** + add fungal coverage if persistently febrile >72h
- **Infectious PPX**: *items with asterisks (*) have well-established benefit and are employed at all institutions*
  - **Bacterial**: cipro 500mg BID or levofloxacin 500mg qd (day -1 to ANC >500)
  - **Viral (HSV/VZV)***: **acyclovir 400mg BID** or famciclovir 500mg BID (day -1 to +365 [auto]; 1y min & until off IS [allo])
  - **CMV**: **letermovir 480mg qd** (dose-reduced w/ cyclosporine) used in CMV-seropositive recipients (day +7 to +100)
    - Alternative: monitor weekly CMV VL (from day -1 to +100), with pre-emptive therapy for CMV viremia with IV ganciclovir or PO valganciclovir
  - **Fungal***: **fluconazole 400mg qd**, vori 200mg BID, posaconazole 200mg TID (day -1 to ANC>500 [auto] or 3-6mo [allo])
    - Anti-mold (vori-, posa-, isavu-conazole) prophlyaxis is considered in patients with AML, lengthy neutropenia
  - **PCP/Toxo***: **Bactrim SS qd** (start after engraftment as outpatient for 6mo [auto], >1y or off IS [allo])

GRAFT-VERSUS-HOST DISEASE MGH Ellucid

- **Acute GVHD**: D0 to +100. ~40% in MRD, ~60% in MUD (cellular immune response, T_H1 cell-mediated) (NEJM 2017;377:2167)
  - Risk factors: ↑HLA mismatch, ↑age, female donor/male recipient, donor parity, TBI-myeloablation, PBSC > BM > CB
  - Cause: (1) Short-lived donor T cells react immediately; (2) Post-engraft, chronic infl → DAMPs/PAMPs → organ damage
  - S/Sx: **skin** (rash, graded by biopsy findings, % body surface, desquamation), **liver** (cholestatic injury, graded by bilirubin), **GI** (diarrhea, graded by volume of diarrhea/day). Grading here.
  - DDx: skin (viral, drug, engraftment), liver (viral, drug, SOS, TPN), GI (*C. diff*, CMV, adeno, GNR, typhlitis, drug)
  - Tx: Grade I topical, II-IV **IV methylpred 1-2mg/kg**; if severe or steroid-refractory: vedolizumab, MMF, ruxolitinib (NEJM 2020;382:1800), antithymocyte globulin (ATG). Trial enrollment for cell therapies (MSCs, Tregs) (Blood 2020;136:410)
- **Chronic GVHD**: 30-70% of patients s/p allo-HSCT (humoral immune response, T_H2 cell-mediated) (NEJM 2017;377:2565)
  - Cause: Pro-inflammatory environment iso graft-vs-tumor response, infx → iatrogenic thymic dysfx in training new T cells + Treg depletion → chronic inflammation w/ T/B cells → aberrant tissue repair after multiple injurious cycles → fibrosis
  - Risk factors: **prior acute GVHD**, HLA mismatch, ↑age, PBSC > BM
  - S/Sx: resembles **scleroderma** (sicca, dysphagia, arthritis, skin tightening, malar rash), lung (bronchiolitis obliterans), liver (cholestasis), cytopenias/immunodeficiency; any organ system (see **NIH consensus scoring sheet** in BBMT 2015;21:389)
  - Tx: **steroid** ± broad immunosuppression, **photopheresis** for skin; novel therapies including ruxolitinib, ibrutinib & belumosudil (ROCK2 inhibitor) have shown responses in steroid-resistant disease; cell therapies (BBMT 2020;26:835)
- **GVHD PPX**: day **-3 to indefinite (tapered over months to years)**, *goal to prevent graft rejection & acute/chronic GVHD*
  - **Immunosuppression regimens**: combined tacrolimus/methotrexate or tacrolimus/sirolimus most common; obinutuzumab
  - **T cell depletion regimens**: (ATG, decreased T-cell dose) no longer favored; ↓chronic GVHD but no effect on OS
  - **Post-transplant cyclophosphamide**: combined with tacro/MMF, used more widely for haplo and MMUD, ↓a/cGVHD

Immunosuppressant	Mechanism	Dosing	Toxicities
Tacrolimus	Calcineurin inhibitor	Trough goal: 5-10ug/L	AKI, ↑K, ↓Mg, ↑LFTs, n/v, TMA, tremor, DM risk
Sirolimus (Rapamycin)	mTOR inhibitor	Trough goal: 3-12ug/L	AKI, sinusoidal obstruction syndrome (SOS), leukopenia, TMA, HLD, cytopenias
Methotrexate (MTX)	Anti-metabolite (inhibits thymidine)	Given on day +1,3,6,11 w/ tacrolimus	**Mucositis**, myelosuppression, hepatitis, AKI
Mycophenolate (MMF/Cellcept)	Anti-metabolite (inhibits purines)	N/A	Myelosuppression, n/v/d
Post-transplant cyclophosphamide (PTCy)	Expands Treg, limits allo-reactivity (JCI 2019;129:2357)	Given days +3 and +4, particularly for haploidentical	**Hemorrhagic cystitis**, mucositis, cardiac toxicity

NON-INFECTIOUS COMPLICATIONS: immune-mediated organ damage, toxic effects of chemo, or immunosuppression

QUICK REFERENCE: MGH ELLUCID (day -8 conditioning to day +30 engraftment)			
Monitor S/Sx	**DDx fever**	**DDx abdominal pain**	**DDx dyspnea/hypoxemia**
• **Chemo toxicity**: mucositis, N/V/D, S/Sx of infection • **GVHD**: rash, jaundice, diarrhea (24h volume) • **SOS**: RUQ pain, jaundice, ascites, edema • **Engraftment syndrome**: fever, dyspnea, edema	• Infection (bacterial, viral, fungal, parasitic) • Drug reaction • Engraftment syndrome (day 7-9 for auto, day 14-21 for allo) • Tumor (initial lysis & cytokine release) • Immobility (aspiration, DVT/PE) • GVHD	• Neutropenic enterocolitis • Colitis: *C. difficile*, CMV • SOS • GVHD • Obstruction, ileus, constipation	• Existing disease: CHF, COPD, asthma • PNA: bacterial, fungal, aspiration • Volume (often on mIVF, transfusions) • Drug: chemo-induced lung injury or cardiotoxicity • Engraftment (pulmonary edema from capillary leak) • Pneumonitis • Alveolar hemorrhage • PE, TRALI, GVHD

- **Pre-Engraftment (day 0-30):** common to have mucositis, nausea/vomiting, alopecia, rash, diarrhea
  - **Mucositis**: most HSCT patients get some degree of mucositis; duration & severity are worse in allogeneic HSCT. Treatment is focused on pain & caloric intake. **WHO grade**: (1) erythema (2) ulcer, solid+liquid PO (3) liquid PO (4) NPO
    - Pain: topical/IV opiates; low threshold for PCA
    - Nutrition: TPN initiated if PO intake impaired by mucositis & expected to continue for ≥1w
    - Palifermin (recombinant keratinocyte growth factor): might reduce duration & severity with select ablative regimens
  - **Engraftment syndrome**: sudden PMN recovery causing cytokine storm and vascular leak
    - S/Sx: fever, rash, weight gain, bone pain; if severe – pulmonary edema, ↑LFTs, AKI, seizures
    - Dx: diagnosis of exclusion (DDx: infection, drug reaction, acute GVHD)
    - Tx: high-dose IV steroids (discuss with attending prior to initiation of steroids)
  - **GI – nausea/vomiting**: optimal management varies based on timing relative to chemo initiation
    - Immediate (day 0-1): 5-HT_3 blockade (Zofran, Aloxi), neurokinin-1 antagonists (Emend), steroid (decadron)
    - Delayed (day 2-5 post chemo): dopamine (D2) blockade (Compazine, Reglan, Haldol)
    - Late (5+ days post chemo): lorazepam, steroids, dronabinol (more helpful in younger pts, marijuana users)
  - **Pulm – idiopathic interstitial pneumonitis/diffuse alveolar hemorrhage (DAH)**:
    - Cause: direct cytotoxic injury to alveoli
    - S/Sx: fever, hypoxemia, diffuse lung infiltrates (**ARDS**)
    - Dx: bronchoscopy w/ serial lavage (r/o infection, blood) – progressively bloodier on serial lavage c/w DAH
    - Tx: high-dose steroids; + for DAH: FFP for INR<1.5, maintain plt >50k; limited data for recombinant FVIIa
  - **Liver – sinusoidal obstruction syndrome (SOS)** (previously called **veno-occlusive disease** [VOD]):
    - Cause: direct cytotoxic injury to hepatic venules leading to hypercoaguable state and microthrombi
    - S/Sx: RUQ pain, jaundice, ascites/edema; ↑ALT/AST/TBili, ↑INR/Cr (if acute liver failure or HRS)
    - Dx: Doppler US c/w reversal of portal vein flow, liver bx; Dx criteria: Tbili >2mg/dL (<21d post-HCT), hepatomegaly/RUQ pain, sudden weight gain (fluid) >2-5% baseline body weight (see criteria and grading: Br J Haematol 2021;190;822)
    - PPX: **ursodiol 300mg TID** (admit to day +30); Tx: **defibrotide**
  - **Renal – AKI** (DDx: ATN, hepatic SOS, aGVHD, thrombotic microangiopathy (TMA), TLS, ABO-mismatched transplant)
    - Nephrotoxins: calcineurin inhibitors, acyclovir, amphotericin, aminoglycosides
    - TMA: subacute onset ~ day 20, caused by endothelial damage 2/2 calcineurin inhibitors, conditioning, & GVHD
    - TLS: considered in pts with significant disease burden at time of transplant; PPX: **allopurinol 300mg qd**
  - **Heme – graft failure, cytopenias, bleeding:**
    - Primary graft failure: persistent neutropenia without engraftment
    - Secondary graft failure: delayed pancytopenia after initial engraftment (immune or infectious)
    - Rx: graft failure may require re-transplantation (CD34 boost); transfusions with irradiated & leukoreduced products
- **Post-Engraftment (day +30):**
  - **PTLD** (post-transplant lymphoproliferative disease): ~1% in allo-SCT; median **day +70-90** (NEJM 2018;378:549)
    - Cause: IS leads to EBV reactivation (dormant in B cells) & clonal B cell proliferation (usually donor-derived)
    - Risk factors: T cell depleted donor graft, treatment with ATG, HLA-mismatch, CB transplant
    - Dx: rising plasma EBV DNA level, biopsy with immunophenotyping for definitive diagnosis
    - Tx: **reduce IS**, anti-viral, rituximab-based chemo (if systemic) vs surgery/RT (if localized), DLI, EBV-targeted T cells
  - **Pulm –** bronchiolitis obliterans (cGVHD), pulmonary veno-occlusive disease
  - **Liver** – cGVHD, drug-induced liver injury, viral hepatitis reactivation, iron overload (secondary hemochromatosis)
  - **Renal** – TMA (chronic onset ~ day 100), drug toxicity (calcineurin inhibitors), nephrotic syndrome

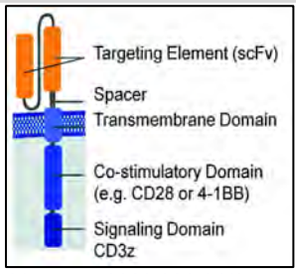
DISEASE RELAPSE: #1 cause of death post-HCT. **Mechanisms**: immune escape, resistant clones that survive conditioning

- Treatment: donor lymphocyte infusion (DLI), salvage chemo, then second allo-HCT, clinical trials for novel therapies, hospice

Oncology

CAR T cell Therapy

Mechanism of Action (NEJM 2018;379:64)



- **Chimeric antigen receptor T cells** autologous cell therapy whereby T cells are collected from patient, genetically modified with construct encoding a chimeric antigen receptor (CAR) that directs T cells against a tumor antigen. CAR T cells are infused into patient, where they persist *in vivo*
- **CAR**: transmembrane engineered protein consisting of extracellular immunoglobulin (antibody)-derived domains (ScFv), which binds a tumor antigen (e.g. CD19). The ScFv is fused to signaling (CD3z) and costimulatory domains (CD28 or 4-1BB) that cause T cell activation and proliferation

FDA-Approved CAR T cell Therapies

- **Yescarta** (axicabtagene ciloleucel - "axi-cel"; anti-CD19, CD28 co-stim domain)
  - Relpased/refractory **large B-cell lymphoma**: ZUMA-1/7 → 82% ORR (54% CR) (NEJM 2017;377:2531, NEJM 2022;386:640)
  - Relapsed/refractory **follicular lymphoma**: ZUMA-5 → 92% ORR (74% CR) (Lancet Oncol 2022;23:91).
- **Kymriah** (tisagenlecleucel - "tisa-cel"; anti-CD19, 4-1BB co-stim domain)
  - Relapsed/refractory **B-ALL** age <25y: ELIANA → 81% CR (NEJM 2018;378:439). Adult phase 2: NEJM 2018;378:449
  - Relapsed/refractory **large B-cell lymphoma:** JULIET → 52% ORR (40% CR), 65% w/o relapse at 1y (NEJM 2019;380:45)
- **Tecartus** (brexucabtagene autoleucel - "brexu-cel"; anti-CD19, CD28 co-stim domain)
  - Relapsed/refractory **mantle cell lymphoma**: ZUMA-2, Phase 2, 93% ORR (67% CR) (NEJM 2020;382:1331)
  - Relapsed/refractory **adult B-ALL**: ZUMA-3 → 71% CR (Lancet 2021;398:491)
- **Breyanzi** (lisocabtagene maraleucel - "liso-cel"; anti-CD19, 4-1BB co-stim domain, 1:1 ratio of CD8+:CD4+ CAR T cells)
  Relapsed/refractory **large B-cell lymphoma**: TRANSCEND NHL 001 → ORR 73% (CR 53%) (Lancet 2020;19;396:839)
- **Abecma** (idecabtagene vicleucel - "ide-cel"; anti-BCMA, 4-1BB co-stim domain)
  - Relapsed/refractory **multiple myeloma**: KarMMa → 73% ORR (33% CR) (NEJM 2021;384:705, NEJM 2023;388:1002)
- **Carvykti** (ciltacabtagene autoleucel - "cilte-cel"; anti-BCMA, 4-1BB co-stim domain, 2 anti-BCMA camelid nanobody domains)
  - Relapsed/refractory **multiple myeloma**: CARTITUDE-1 → 98% ORR (83% CR), 27-month PFS 55% (Lancet 2023;41:1265)
- Under investigation: combo w/ PD1-axis blockade (Cancer Cell 2019;36:471) & other cell types, e.g. CAR-NK cells (NEJM 2020;382:545)

Toxicities (JNCCN 2024; BBMT 2019;25:625)

MGH Ellucid

- **Cytokine-release syndrome (CRS)**
  - At least Grade 1 occurs in majority of patients, <10% Grade 3. Typically 1-3d (up to 10-15d) post-infusion, lasts ~7d. Caused by cytokine release (IL-2, sIL2R, IFNγ, IL-6, GM-CSF) triggered by CAR T cell engagement of antigen and *in vivo* expansion. ↑risk: bulky disease, baseline ↓platelets, ↑CRP. Axi-cel > Tisa-cel
  - **Signs/Sx**: fever, ↓BP, ↑HR, ↓SpO_2, malaise, rigors, anorexia, myalgia. Can affect any organ (CV, lung, GI/liver, renal, CNS), arrhythmias, capillary leak syndrome, HLH
  - **Dx**: monitor for 7d post infusion for FDA-approved therapies (inpt or possibly close outpt); VS, basic labs, ferritin, coags, CRP, TLS labs. When suspicious, make sure to rule-out infection
  - **Tx**: **See table.** Tocilizumab (anti-IL6R) 8mg/kg over 1h (≤800mg); siltuximab (anti-IL6) and/or anakinra (anti-IL1R); 2nd line: steroids. if plan to treat CRS with steroids or anti-IL6, ****first get clear approval by the treating attending** (even if overnight).
  - Broad-spectrum antibiotics (cefepime) if fever + neutropenia
- **Immune effector cell-associated neurotoxicity syndrome (ICANS)**
  - **Etiology**: unclear; cytokine diffusion into brain (IL-1, IL-6, IL-15 a/w neurotoxicity), BBB disruption, CAR T cell trafficking to CNS
  - **Timing**: typical onset 4-10d post-infusion, duration variable (14-17d). Can occur w/ or after CRS, but CRS is not req. for ICANS.
  - **S/Sx**: aphasia, impaired fine motor skills, seizure, motor weakness, toxic encephalopathy (see ICE & ICANS grade), rare parkinsonism w/ BCMA CAR T cells (Nat Med 2021;27:2099)
  - **Dx**: neuro c/s, ICE score, ICANS grade. If grade ≥3: MRI brain w/ w/o contrast, EEG, LP (r/o infection, e.g. HHV6), fundoscopy
  - **Tx: See table.** Seizure prophylaxis starting on day of infusion (levetiracetam 500-750 mg q12h for 30d). Generally, dexamethasone +/- anakinra, treat CRS if present (i.e. toci), but ****first get clear approval by the attending** (even if overnight)
  - **Prognosis**: generally reversible, rare fatal cases
- **Persistent Hematologic Toxicity**
  - Can cause grade ≥3 anemia, neutropenia, thrombocytopenia, and B-cell aplasia that persists months-years
  - Mechanism unclear, a/w with decreased baseline hematopoietic reserve and inflammation (Blood 2021;138: 2499)
- **Hemophagocytic Lymphohistiocytosis Like Syndrome (IEC-HS):** Rare, 1% develop (see Anemia) (TCT 2023 HLH guidelines)

ASTCT CRS Grade		Treatment**
1	**Fever** (≥38C)	Tylenol, supportive. If >3d, consider tocilizumab
2	Fever & **HoTN** not requiring pressors or hypoxemia on NC	**Tocilizumab** q8h PRN up to x4, add steroids as below if still ↓BP after 1-2 doses, IV fluids
3	Fever + ↓BP requiring **pressor** or ↓SpO_2 requiring **HFNC, NRB**	**Tocilizumab** as above, **dexamethasone** 10mg IV q6h (or equivalent)
4	Fever + ↓BP requiring **multiple pressors** or ↓SpO_2 requiring **BIPAP, MV**	**Tocilizumab + dex** as above. If refractory, consider **methylpred** 1g/d IV x3d w/ taper

Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool	
Max score: 9	A&Ox3 [+ hosp] (4 pts), naming [clock, pen, button] (3 pts), follows commands (1 pt), writes sentence (1 pt), serial 10s from 100 (1 pt)

ASTCT ICANS Grade		Treatment**
Grade 1	ICE = 7-9, awakens spontaneously	Supportive
Grade 2	ICE = 3-6, awakens to voice	Dex 10mg IV x1
Grade 3	ICE = 0-2, awakens to tactile stimulus, or focal edema on neuroimaging, or brief seizure	Dex 10mg IV q6h or methylpred 1mg/kg IV q12h
Grade 4	ICE = 0, unarousable, seizure >5min or w/o return to b/l, or deep focal motor deficit, or diffuse cerebral edema, or ↑ICP	Methylprednisolone IV 1g/d x3d or equivalent w/ taper. Can add anakinra if no response

Oncology

Solid Organ Malignancies

Organ	Risk factors/screening	Diagnostics	Treatment
Breast ▪ Infiltr. ductal (70-80%) ▪ Invas. lobular (5-10%) ▪ Mixed ductal/lobular (7%) ▪ Mucinous (2%) ▪ Tubular (1.5%) ▪ Medullary (1%) ▪ Papillary (1%) NCCN Guidelines Breast Cancer 2024	**Risk factors**: Age, genetics (*BRCA1/2*, *CHEK2*, *ATM*, *PALB2*), FHx, obesity after menopause, menopause >55, chest RT, 1st birth >30, nulliparity, HRT, menarche <13y, EtOH, benign breast disease, tobacco, DES exposure **Screening**: ▪ USPTF: q2y mammo 40-74 ▪ NCCN: q1y mammo >40 or 10y before earliest FHx if >30 or 10y after RT if >30	▪H&P ▪Dx bilateral mammogram (Bi-RADS), US, FNA or core Bx (> excis. Bx), breast MRI if young or to assess extent (good Sn, but Sp 72%) ▪Path review (include Ki-67) ▪Genetic testing and counselling	**Early stage** (I, IIA, IIB through T2N1): ▪ Breast Conserving Surgery ± RT (NEJM 2023;388:585) vs. mastectomy ± RT, HR tx, HER2 tx, chemo if high risk **Locally advanced** (Stage IIB T3N0, IIA-IIIC): ▪ Surgery + RT w/ (neo)adj. chemo & HR/HER2 tx **(Neo)adjuvant therapy**: ▪ **ER/PR+, HER2-**: tamoxifen or aromatase inhibitors (AI) (anastrozole, letrozole, exemestane); no AI if premenopausal; ± ovarian suppression if high risk. Chemo: AC-T (doxo, cyclophos [CYC], paclitax.) or TC ▪ **HER2+**: TCH(P) (trastuzumab, carboplatin, docetaxel, ± pertuzumab) or ACTH(P) (doxorubicin, CYC, paclitaxel, trastuzumab ± pertuzumab) + ER/PR tx if HR+ ▪ **Triple Neg** (NEJM 2017;372:2147): capecitabine **Metastatic/recurrent** (Stage IV): ▪ **ER+**: as above ± fulvestrant (ER antagonist); ± CDK4/6 inhibitor or everolimus (mTOR inhibitor) ▪ **HER2+**: THP (1st line) or T-DM1 (trastuzumab-drug conjugate), trastuzumab+lapatinib ▪ **BRCA mutation** (NEJM 2017;377:523; NEJM 2018;379:753): olaparib or talazoparib ▪ **Triple neg:** systemic tx
Colon and rectum ▪ AdenoCa (98%) ▪ Neuroendocrine ▪ Lymphoma NCCN Guidelines Colon Cancer 2024	**Risk factors**: ▪ FHx, genetic (FAP, HNPCC, PJS), IBD (UC>CD), obesity, tobacco, red/processed meat, EtOH, adenomat. polyps, age ▪ ↑death w/ R-sided (JAMA Oncol 2018;4:e173695) **Protective factors**: ASA for 50-59yo and ≥10% CVD risk (Annals 2016;164:814) **Screening (45-75yo)**: colo, flex sig, CT colo, FIT, FOBT for 50-75yo	▪ Colonoscopy w/ polyp, bx for path ▪ CT C/A/P, CEA ▪ MRI for liver mets ▪ Pelvic MRI or endorectal US for rectal CA ▪ **Genetic testing**: MSI/MMR status in all, K/N-RAS, BRAF, HER2	**Colon**: **I-IIA**: surgery + observation, or capecitabine or 5-FU/leucovorin (IIA) **IIB-IV**: surg, RT, **systemic tx**: FOLFOX (oxaliplatin, leucovorin, 5-FU), CAPEOX (capecitabine, oxaliplatin), FOLFIRI (irinotecan, leucovorin, 5-FU), FOLFOXIRI (irinotecan, oxaliplatin, leucovorin, fluorouracil), ± bevacizumab; nivo ± ipi or pembro ▪ **BRAF V600E**: encorafenib + EGFR inhib. (cetuximab, panitumumab) ▪ **MSI-H/dMMR**: immuno tx (pembro, nivo, ipi) ▪ **HER-amp +RAS/BRAF WT**: trastuzumab + pertuzumab/lapatinib ▪ **Rectal**: low anterior (LAR) v abdominoperineal resection (APR) ± neo v adj chemoRT. Chemo as in colon cancer
Lung ▪ NSCLC (84%): adeno, large>SCC ▪ SCLC (13%) NCCN Guidelines NSCLC 2024 NCCN Guidelines SCLC 2024	**Risk factors** (Nat Rev Ca 2007;10:778): ▪ Age, male, tobacco, asbestos, occup. exposures, lung fibrosis or COPD, prior cancer history, exposure to infectious agents (TB, fungal) ▪ 25% lung cancer worldwide not due to smoking → more likely to have single mutation **Screening** (Annals 2014;160:330): ▪ Annual low dose CT chest for 50-80 yo current smokers with ≥20 pack-year hx OR quit within last 15 yrs	▪ CT C/A/P, FDG-PET/CT, brain MRI ▪ PFTs ▪ Evaluate pathologic LNs with biopsy ▪ Molecular testing for NSCLC (*EGFR*, *ALK*, *ROS1*, *NTRK1/2/3*, *MET* exon14 skipping, *RET*, PD-L1) before systemic tx	**NSCLC**: **IA**: surgery ± RT; **IB-IIIA**: surgery if able ± adjuv chemoRT ± osimertinib or atezolizumab. **IIB/IIIA unresectable, IIIB**: definitive chemoRT + adjuvant durvalumab (NEJM 2018;379:2342). **IV**: systemic tx as below: ▪ **ChemoRT**: cisplatin + docetaxel/etoposide/ pemetrexed; carboplatin + pemetrexed/paclitaxel/ gemcitabine/docetaxel ▪ **Targeted inhibitors**: *EGFR* (osimertinib 1st line, erlotinib, afatinib, gefitinib, dacomitinib); *ALK/ROS1* (alectinib, crizotinib, ceritinib, brigatinib, lorlatinib); *BRAF/MEK* (dabrafenib/trametinib); *TRK* (larotrectinib, entrectinib) ▪ **Immunotherapy** (PD-L1+) (Lancet 2016;387:1540; NEJM 2018;378:2078): pembro ± chemo. ipi/nivo, atezolizumab+ platinum+ taxane + bevacizumab (anti-VEGF) **SCLC**: ▪ **Limited**: surgery + chemo ± mediastinal RT ▪ **Extensive** (NEJM 2018;379;2220): chemo & atezolizumab v durvalumab ± RT for lobar obstruction, SVC syndrome, bone/brain mets ▪ **Chemo**: platinum agents, etoposide, irinotecan

Oncology

Solid Organ Malignancies

Organ	Risk factors/screening	Diagnostics	Treatment
Melanoma ▪ Superficial spreading (75%) ▪ Nodular (15-30%) ▪ Lentigo maligna (10-15%) ▪ Acral lentiginous (<5%) ▪ Amelanotic (2-10%) ▪ Ocular (5%) ▪ Mucosal (~1%) NCCN Guidelines Cutaneous Mel 2024 NCCN Guidelines Uveal Mel 2024	**Risk factors**: ▪ Sun exposure (UVB > UVA), atypical nevi, high nevi count, FHx or personal hx, immunosuppression ▪ Familial melanoma with germline *CDKN2A*, *CKD4*, *POT1* mutations **Most common somatic mutations**: ▪ *BRAF* (V600E, V600K) 50%, *NRAS* 15-20%, *KIT* 10-15% (acral). Genetic testing for stage II-IV disease	▪ Biopsy of primary tumor (Breslow depth prognostic), LN sampling, CT C/A/P, brain MRI, & serum LDH for active surveillance and treatment response ▪ Liver MRI for ocular/uveal melanoma – liver most common metastatic site	**Localized disease:** wide excision of primary tumor ± sentinel lymph node biopsy. Topical imiquimod or RT if surgery contraindicated or as adjuvant tx. **Metastatic disease:** Systemic therapy ± excision (if feasible) ± RT (for sympt. localized disease, e.g. brain mets) ± talimogene laherparepvec (T-VEC, intralesion injection of HSV → tumor cell lysis & GM-CSF expression) (JCO 2015;33:2780). Systemic therapy: ▪ *Immunotherapy* (NEJM 2015;373:23; NEJM 2015;372:2521): anti-PD-1 (pembro/nivo); anti-CTLA4 (ipilimumab), ipi+nivo (NEJM 2019;381:1535) ▪ *Targeted tx* (NEJM 2014;371:1867): If BRAF/MEK mutated, combo inhibitors(dabrafenib+trametinib, vemurafenib+cobimetinib, encorafenib+binimetinib). If KIT mutant, imatinib.
Pancreas ▪ Exocr./adeno (~95%) ▪ Endocrine (<5%) NCCN Guidelines Pancreatic 2024	**Risk factors**: ▪ Tobacco, EtOH, obesity, DM, chronic pancreatitis, age, male, FHx, HNPCC, chemical/heavy metal exposure, germline mut. (*BRCA1/2, TP53, STK11, MLH1, MSH2/6, PMS2, CDKN2A*). **Genetic mutations**: ▪ *KRAS*, *TP53*, *SMAD4*, *TGFbR1/2*, *CDKN2A*, *MLL2/3*, *KDM6A*, *ATM*, *NTRK*, *ALK*, *ROS1*, *BRAF*, *HER2*, *PALB2*	▪ CT C/A/P pancreas protocol, EUS+Bx, MRCP ± ERCP, MRI for indeterminate lesions, PET/CT in high risk patients ▪ CA19-9, LFT ▪ Germline testing +molecular profiling of tumor tissue ▪ Bx metastatic site if metastatic disease	▪ **Resectable/Borderline**: surgery ± systemic tx: 1st line FOLFIRINOX (leucovorin, 5-FU, irinotecan, oxaliplatin), gemcitabine+nab-paclitaxel, gem+capecitabine, ± chemoRT ▪ **Locally advanced**: systemic tx as above or stereotactic body radiation (SBRT) ▪ **Metastatic**: systemic tx ±: • **BRCA1/2:** olaparib (NEJM 2019;381:317); • **NTRK fusions**: larotrectinib, entrectinib • **MSI-H/dMMR/TMB-H:** pembrolizumab (NEJM 2015;372:2509) • **BRAF V600E:** dabrafenib + trametinib
Prostate ▪ Adenocarcinoma (95%) ▪ Transitional, basal cell, intraductal carcinomas; neuroendocrine, carcinosarcoma, lymphoma, stromal sarcoma NCCN Guidelines Prostate Cancer 2024	**Risk factors**: ▪ Age, black race, genetic factors (*BRCA1/2* and family history), smoking **Screening with PSA**: ▪ 55-69: individualized risk-benefit discussion ▪ 70 and above: no testing (JAMA 2018;319:1901)	**Diagnosis**: **Bx** **After diagnosis**: ▪ TRUS, MRI, biomarkers, CT C/A/P, bone scan **Germline testing**: ▪ High/very high NCCN risk ▪ Any risk level if ⊕ FHx or intraductal histology	**Low risk**: surveillance (PSA, DRE ± Bx) vs external beam radiation therapy (EBRT) ± brachytherapy (BT) vs radical prostatectomy **Intermediate/high risk**: combination of EBRT, BT ± prostatectomy w/ lymph node dissection, and androgen deprivation therapy (ADT): *Orchiectomy, Androgen R blocker*: enzalut-, apalut-, darolut-, flutamide. *Androgen synthesis inhib*: abiraterone. *GnRH agonist*: leuprolide, gose-, hist-, triptorelin, *GnRH antagonist*: degarelix, relugolix **Metastatic/recurrent**: ADT, if fail, ADT+doxetaxel. Bone mets: radium-223 or denosumab/zoledronic acid, palliative RT. MSI-H/dMMR: pembro
Cancer of Unknown Primary ▪ Adenocarcinoma or carcinoma not otherwise specified (85%) ▪ Squamous cell carcinoma (5%) ▪ Undifferentiated carcinoma (5%) ▪ Neuroendocrine tumors (5%) NCCN Occult Primary Guidelines 2024	**Pathologic Diagnosis**: ▪ Core needle biopsy (preferred) and/or FNA from most accessible site ▪ MSI/MMR testing **Initial Evaluation**: ▪ Immunohistochemistry ▪ Gene expression profiling ▪ Tumor serum markers: β-hCG (testicular), AFP (testicular, hepatocellular carcinoma), CEA (CRC), CA-125 (ovarian)	**Workup**: ▪ Complete H&P (breast, GU, pelvic, rectal, skin exams) ▪ Routine labs (CBC, electrolytes, LFT, Cr) ▪ Occult blood stool testing ▪ CT C/A/P with IV contrast +/- PET ▪ Endoscopy, UA, LDH (if indicated)	**Adenocarcinoma:** paclitaxel + carboplatin ± etoposide; gemcitabine + cisplatin or docetaxel; capecitabine + oxaliplatin (CapeOx); fluorouracil + leucovorin + oxaliplatin (FOLFOX) or irinotecan (FOLFIRI); docetaxel + carboplatin or cisplatin **Squamous cell carcinoma:** Paclitaxel + carboplatin or cisplatin; gemcitabine + cisplatin; docetaxel + carboplatin or cisplatin; cisplatin + fluorouracil; docetaxel + cisplatin+ fluorouracil (DCF) **Adenocarcinoma and SCC**: capecitabine, fluorouracil, pembrolizumab, selpercatinib **Neuroendocrine tumors:** paclitaxel + carboplatin + etoposide; cisplatin + etoposide; temozolomide ± thalidomide.

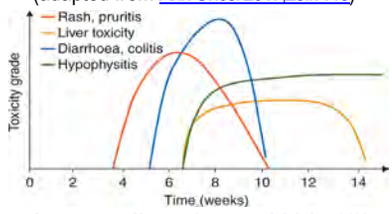
IMMUNE CHECKPOINT INHIBITORS (ICI)

- **Mechanism of Action**: Block receptors that down-regulate T cell activation → CTLA-4, PD-1 (on T-cell) or its ligand PD-L1 (on cancer cell) → ↑antitumor immune response (Nat Rev Clin Oncol 2016;13:473; NEJM 2018; 378:158; NEJM 2016;375:1767)
- **Indications**: >20 cancers. PD-1i FDA-approved for ***any*** microsatellite instability-high (MSI-H) or mismatch-repair deficient tumors (dMMR). Pre-existing autoimmunity not absolute contraindication, but can flare (JCO 2018;36:1905; Ann Oncol 2017;28:368)

IMMUNE RELATED ADVERSE EVENTS (IRAEs) (NEJM 2018;378:158; Ann Oncol 2017;28:iv119; J Immunother Cancer 2017;5:95)

- **Definition**: Systemic autoimmune/inflammatory event 2/2 immune activation by ICI
- **Grading**: 1-4 (mild to life threatening), guides treatment regimen
- **Risk factors**: Combination (anti-CTLA-4 + anti-PD-1) a/w earlier onset, ↑incidence and severity; anti-CTLA-4 > anti-PD-1
- **Timing**: Highly variable, can present weeks-years after use
- **Tx**: Based on expert consensus (ASCO J Oncol Pract 2018;14:247). 1st line corticosteroids. If refractory: infliximab, MMF, tacrolimus, MTX, ATG, tocilizumab. IVIg/plasmapheresis in autoAb-mediated/neurologic irAEs

Timing of irAE after ipilimumab
(adapted from Ann Oncol 2017;28:iv119)



- **Impact**: IRAEs associated with improved OS in ICI therapy, even in context of hospitalization for toxic effects (JAMA 2024;7(1))

SELECTED IRAE DIAGNOSIS, GRADING, AND MANAGEMENT (ASCO: JCO 2021;39:4073; NCCN Guidelines 2024)

Consult SIC (Severe Immunotherapy Complications) Service for inpatient questions regarding concern for IRAEs

Skin toxicity: Common, 30-40% of pts (CTLA-4 > PD-1/L1 blockade). Rash, pruritis, bullous derm, lichen planus, psoriasis, rarely SJS/TEN/DRESS. Vitiligo seen in melanoma, rarely in other cancers, a/w response to immunotherapy (JAMA Dermatol 2016;152:45)

- **Timing**: Early, within the first few weeks after tx initiation
- **S/Sx**: Four types (1) Inflammatory: psoriasiform or lichenoid reactions; (2) Immunobullous: dermatitis herpetiformis or bullous pemphigoid; (3) Keratinocyte alteration: acantholytic dyskeratosis; (4) Immune reaction mediated by alteration of melanocytes
- **Dx**: exam; r/o other etiologies (infection, DRESS, SJS/TEN); grading based on BSA (<10% Gr 1, 10-30% Gr 2, >30% Gr 3)
- **Tx**: topical steroids, oral antihistamines for inflammatory/pruritic reaction. If severe, consider systemic steroids + derm c/s

Colitis: More common w/ anti-CTLA-4; grade 3/4 colitis is higher with ipilimumab (<10%) than with anti-PD-1 agents (1-2%).

- **Timing**: 6-8w after initiation of therapy
- **S/Sx**: Diarrhea, weight loss, abdominal pain/urgency/rectal bleeding if severe
- **Dx**: Lactoferrin/calprotectin; r/o other etiologies (*C diff.*, stool Cx, CMV PCR). CT A/P can show mild diffuse bowel thickening or segmental colitis. EGD/flex sig/colo for Grade ≥2 sx, path w/ active acute colitis.
- **Tx**: Antidiarrheal agents, budesonide 9mg PO or prednisone PO vs. high dose steroids w/ taper, infliximab in refractory cases

Pneumonitis: More common w/ anti-PD-1, serious toxicity rare. Higher risk w/ combination or targeted therapy (Chest 2017;152:271)

- **Timing**: Highly variable, can be later
- **S/Sx**: Dyspnea, cough, fever, AIP/ARDS; 1/3 asymptomatic (JCO 2017;35:709; Clin Cancer Res 2016;22:6051)
- **Dx**: Rule out other etiologies, consider BAL, PCP, CT often non-specific though can show GGOs and/or nodular infiltrates
- **Tx**: Oxygen, glucocorticoids w/ prolonged taper, diuresis, infliximab, mycophenolate mofetil or IVIg if severe or refractory

irAE Severity	Management
Grade 1	• Continue checkpoint inhibitor • Increased monitoring • Supportive care
Grade 2	• Delay checkpoint inhibitor • Oral corticosteroids (0.5-1 mg/kg) as outpatient, taper over 2-4 wks • Re-challenge with ICI if returned to grade 1 toxicity • Increased monitoring
Grade 3	• Delay checkpoint inhibitor, consider rechallenge if benefits outweigh risks • Oral corticosteroids (1-2 mg/kg) as outpatient, IV if symptoms persist 48-72 hours, taper over 4-6 wks • Consider organ specialist consultation (GI, pulm, etc.)
Grade 4	• Discontinue checkpoint inhibitor (except for endocrinopathies managed with hormone replacement) • Hospitalize for IV steroids • Consider additional immunosuppressive agents if no response to IV steroids • Consult organ specialist

Hypophysitis (JAMA Oncol 2018;4:173): Primarily w/ anti-CTLA-4 (3%), rarely w/ anti-PD-1/PD-L1 (0.5%). Mechanistically distinct from other irAEs; possibly by direct binding of ipilimumab to CTLA-4 on normal cells of anterior pituitary (Sci Transl Med 2014;6:230).

- **Timing**: Median onset ~8w
- **S/Sx**: HA (common, can be severe), fatigue, n/v, dizziness, weight changes, hot flashes, cold intolerance, hyponatremia (anterior hypopituitarism), vision changes; usually without central diabetes insipidus (posterior pituitary spared)
- **Dx**: MRI brain/pituitary shows diffuse pituitary enlargement (generally resolves by 2mo); test hormonal axes: 8AM serum cortisol + ACTH and/or cort stim; TSH w/ FT4/total T4/T3; PRL; LH/FSH, serum testosterone/SHBG (in men); IGF-1
- **Tx**: Hormone substitution: **Hypocortisolism**: glucocorticoid replacement (prednisone 3-5mg daily) (Cancer 2018;124:3706; Oncologist 2016;21:804)**. Central hypothyroidism**: levothyroxine. **Hypogonadism**: consider testosterone replacement. **GH deficiency**: GH theoretically contraindicated due to active malignancy, although little clinical evidence

Myocarditis (JACC 2018;71:1755): Rare but serious AE a/w high mortality (46% in severe myocarditis); risk higher w/combo tx

- **Timing**: Generally within 3mo (Oncologist 2018;23:874; Lancet 2018;391:933)
- **S/Sx**: Heart failure, arrhythmia (high grade AV block, ventricular tachycardia)
- **Dx**: CK, EKG, **troponin**, NT-proBNP, TTE, MRI and EMG ± endomyocardial Bx
- **Tx**: Discontinuation of ICI; high dose or pulse-dose steroids (1g IV, then PO pred 1mg/kg) (J Am Heart Assoc 2020;9:2); 2nd-line consider ATG/IVIg or infliximab/MMF/tacro (Oncologist 2018;23:879). GDMT for HFrEF. PPM for new conduction delay.

Other irAEs (JCO 2019;36:1714): Inflammatory arthritis/myositis, PMR/GCA, nephritis, pancreatitis/DKA, adrenal insufficiency, hepatitis/cholestasis, myasthenia gravis, GBS, peripheral/autonomic neuropathy, aseptic meningitis, encephalitis/ADEM, optic neuritis, traverse myelitis, AIHA, ITP, TTP/HUS, aplastic anemia, acq. hemophilia, pericarditis, uveitis/iritis, episcleritis, blepharitis

TUMOR LYSIS SYNDROME (NEJM 2011;364:1844; JCO 2008;26:2767)

- **Pathophys**: TLS 2/2 tx initiation or spontaneous in cancers w/ high turnover → release of intracellular metabolites (i.e. uric acid, K+, phos) → AKI (uric acid causes renal vasoconstriction, precipitates in tubules), seizure, CaPhos crystal deposition (↑phos → ↓Ca)
- **Presentation**: ↓UOP, weakness/cramps/tetany/perioral numbness, seizure, arrhythmia
- **Risk factors**: high risk: ALL/AML (WBC ≥100k), CLL (on venetoclax & ↑uric acid), stage 3/4 Burkitt/lymphoblastic NHL, bulky DLBCL; intermediate risk: ALL (WBC <100k), AML (WBC 25-100k or <25k & ↑LDH), Burkitt, DLBCL, CLL (chemo-specific & ↑WBC), rare chemo-sens bulky solid tumor; low risk: HL, indolent NHL, CML, CLL (on alkylating tx & WBC <50k), MM
  - High risk substrate: WBC >50k, LDH >2x ULN, bulky tumor (>10cm), hypovolemia, uric acid >7.5, renal failure
- **Labs/workup**: BMP (electrolytes, Cr, iCal), Mg, phos (calculate Ca-phos product), uric acid, LDH, CBC/diff, ECG
- **Diagnosis (Cairo-Bishop criteria)**:
  - Laboratory diagnosis: ≥2 criteria within 3d before or 7d after cytoxic therapy: uric acid ≥8mg/dL, K ≥6mEq/L, phos ≥4.5mg/dL, or Ca ≤7mg/dL. Criteria also satisfied if 25% change from baseline.
  - Clinical diagnosis: laboratory dx & ≥1 clinical criteria: Cr 1.5x ULN, arrhythmia, or seizure
- **Prophylaxis and treatment**: while treating, labs q2-4h & telemetry (electrolyte abnormalities)
  - **Hydration**: 2-3L/m^2 per day. D5-1/2NS or NS if hyponatremic/hypovolemic. Maintain **UOP ≥100cc/hr** for excretion of uric acid and phos; diuretics PRN (prefer loops to ↓K) to maintain UOP and treat hypervolemia
  - **Urinary alkalinization**: w/ NaHCO3, only indicated if metabolic acidosis when not using rasburicase, contraindicated in hyperphos (↑CaPhos precip). Not common practice at MGH.
  - **Treat abnl electrolytes**: hyperK tx (e.g. lokelma, lasix, insulin, RRT), phos binders, **delay tx of hypoCa** until phos normalizes or hypoCa/hyperK is severe (tetany/arrhythmia) to avoid ↑CaPhos precip
  - **Allopurinol** (↓uric acid formation): 300-600mg/day (adjust dose if renal dysfunction). Can also utilize febuxostat in renal dysfunx.
    - ↓ clearance of other meds (cyclophosphamide, MTX, 6-MP, azathioprine, ampicillin)
    - *HLA-B*5801* ↑prev. in Southeast Asian, black pts, ↑**risk of SJS/TEN**, consider testing (ACR guidelines) + alternative tx
  - **Rasburicase** (↑uric acid clearance; discuss w/ attending): 0.2mg/kg IV (but 3-6mg IV usually effective), administer if high risk, baseline renal failure, ↑baseline or rising uric acid >7.5 or Cr despite allopurinol/saline, or cannot hydrate (volume overload)
    - Risk of anaphylaxis, methemoglobinemia. **Contraindicated in G6PD deficient** (can cause hemolysis); **check G6PD early**
  - **Renal replacement therapy**: indicated if Ca-phos product ≥70mg^2/dL^2 (albumin-corrected Ca × phos)

HYPERVISCOSITY SYNDROME/LEUKOSTASIS (Blood 2012;119:2205; Blood 2018;132:1379)

- **Etiology**: (**1**) ***hyperproteinemia*** from monoclonal gammopathies (Waldenström's macroglobulinemia [IgM] > MM [IgA>IgG]) or polyclonal (cryoglobulins, HIV, Sjögren's, ↑RF, IgG4, IVIg or rituximab) (**2**) ***hyperleukocytosis/leukostasis*** seen in AML/ALL with blasts >50k (leukostasis rare in CLL unless very high counts >400k WBC) (**3**) *other:* polycythemia vera, sickle cell, spherocytosis
- **S/Sx**: pulm (SOB, infiltrates) & CNS (blurry vision 2/2 retinal vein engorgement, HA, dizziness, ataxia, confusion, coma), fever, epistaxis → page **Heme/Onc fellow** & **Clin Path resident** for **emergency viscosity study**, notify attending to discuss pheresis
- **Diagnosis**: serum viscosity (↑Ostwald tube), SPEP, SFLC, **WBC (often >100k, but can be lower if AML/ALL blast crisis)**
  - Lab artifacts from hyperleukocytosis: **spurious ↑K** (use blood gas K), **falsely low arterial pO_2** (use pulse oximeter)
- **Treatment**: always start with plasma volume expansion with **IV NS**
  - *Hyperproteinemia:* **plasmapheresis** (aiming for resolution of symptoms); reduces viscosity by 20-30% per session
  - *Leukostasis*: **leukapheresis**; cytoreduce (**hydroxyurea**); **induction chemo**; **avoid RBC & plt transfusion** (↑viscosity)

METASTATIC EPIDURAL SPINAL CORD COMPRESSION (Seminars in Neurology 2010;30:245; Lancet Neurology 2008;7:459)

- **Primary CA**: lung, prostate, breast > non-Hodgkin's lymphoma, renal cell, multiple myeloma, Hodgkin's lymphoma
- **Location**: T (60%) > L (25%) > C (15%); multiple sites in 30%; ESCC score for spinal level (JNCCN 2016;14:70)
- **S/Sx**: back pain (usually 1st sx; radicular, localized, worse at night/recumbent/valsalva) → weakness, gait instability → sensory deficits (ascending numbness, saddle anesthesia in cauda equina), bowel/bladder dysfunction (urinary retention, incontinence)
- **Exam**: pain precedes other sx by ~7w, weakness/ataxia, paresthesia, ↑reflexes, ⊕ Babinski, ↓anal sphincter tone
- **Diagnosis**: STAT total spine MRI with cord compression/metastasis protocol, CT myelography if MRI not possible
- **Treatment**: call Spine Surgery & Radiation Oncology ASAP → more effective than chemo (except for heme, germ cell malignancies)
  - Neuro deficits/pain: **dexamethasone 10mg x1 IV**, then 16mg PO daily (divided), taper once definitive tx

BRAIN METASTASES WITH INCREASED INTRACRANIAL PRESSURE (Ann Palliat Med 2015;4:225; JCO 2015;33:3475)

- Intracranial tumors present in ~10-30% of patients with metastatic disease; call Neurosurgery & Radiation Oncology
- **Primary CA**: lung > breast > melanoma > RCC, osteosarcoma, head and neck, thyroid, colorectal
- **S/Sx**: HA (40-50%; "tension", bifrontal, worse w/ Valsalva and forward bending, n/v), focal neuro deficits (20-40%, hemiparesis most common), cognitive dysfunction (30-35%), new onset seizures (10-20%), stroke (5-10%)
- **Diagnosis**: MRI w/ contrast > non-enhanced MRI or CT with contrast.
- **Treatment**: control vasogenic edema (**dexamethasone 10mg IV x1, then 4-8mg IV/PO BID**), consider AED (usually not for 1° ppx); avoid AC if concern for active hemorrhage; definitive treatment will ↓local recurrence: for multiple mets, stereotactic radiosurgery > whole-brain XRT (↑neurocognitive impairment can be mitigated w/ hippocampal avoidance/memantine) > surgery

SUPERIOR VENA CAVA (SVC) SYNDROME (NEJM 2007;356:1862; Mayo CP 2017;92:609)

- **Etiology**: external compression of SVC from mediastinal mass (commonly lung CA or NHL) causing ↑upper body venous pressure
- **Symptoms**: cerebral edema (HA, confusion, herniation), narrowing of larynx/pharynx (dyspnea, stridor, cough, dysphagia, hoarseness), head/neck swelling (visually striking, often not clinically significant), hemodynamic instability (↓venous return)
- **Diagnosis**: CT venography (SVC syndrome protocol), **obtain/ensure tissue diagnosis ASAP to guide definitive tx**
- **Treatment**: secure airway, RT/chemo, intravascular stent (emergent/refractory), steroids (stridor/resp distress only, d/w attending)

Oncology Febrile Neutropenia

DEFINITIONS AND ETIOLOGY (J Oncol Pract 2019;15:19; NCCN Prevention and Treatment Guidelines)

- **Definition**: **T ≥100.4 (**≥1hr or oral >100.9) with **ANC <500cells/mL** or **expected to decrease** to <500 over the next 48h
  - Functional neutropenia: defective PMNs, common in leukemia (↓neutrophil function despite ANC>500)
- **Microbiology**: ~40-50% have infectious source identified; others attributed to translocation of intestinal bacteria
  - When organisms identified: 40% GNRs (E. coli, Klebs > PsA); 60% GPCs (CoNS > MSSA/MRSA, strep, enterococcus/VRE) esp w/ indwelling lines or mucositis; fungal (Candida, Aspergillus) more likely w/ prolonged ↓ANC, broad-spectrum abx use, or TPN

EVALUATION

- **H&P**: prior micro data, time since last chemo, recent antibiotic therapy/ppx, major comorbid illness, use of devices
- **Exam**: mouth (mucositis), skin, perineum/rectal (**visual inspection**, **avoid DRE**), indwelling lines/port (erythema/tenderness)
- **Studies**: BCx x2+ sites (≥1 periph, 1 per CVC lumen), UA/UCx, CXR, SCx/GS, resp viral panel/COVID-19 PCR, CMV PCR (SCT)
  - Fungal markers: LDH, β-D-glucan; galactomannan if high risk for Aspergillus (SCT, GVHD, neutropenia >10-14d)
- **Further site-specific studies to consider**:
  - GI symptoms: CT A/P (evaluate for neutropenic colitis/typhlitis); stool culture, O&P, C. diff if diarrhea
  - Pulmonary symptoms: CT chest ± bronch/BAL (especially if prolonged F&N)
  - Headache/sinus pain: CT face/sinus
- **Risk stratification**: (J Oncol Pract 2019;15:19; NCCN Prevention and Treatment Guidelines)
  - **MASCC Risk Index** (JCO 2000;18:3038) and **CISNE** (JCO 2015;33:465) can measure risk of F&N-related complications
  - **High risk**: anticipated ANC ≤100 for ≥7d, inpt status, co-morbidities/infections (renal/hepatic impairment, PNA, central line infxn), allogeneic HCT, mucositis grade 3-4, alemtuzumab use or CAR-T within past 2mo → inpatient management
  - **Low risk** (JCO 2018;36:1443): anticipated ANC ≤100 for <7d, no co-morbidities, good performance status (ECOG 0-1), strong home social support → treated with PO antibiotics after brief inpatient stay versus strictly outpatient

TREATMENT/PROPHYLAXIS

- **MGH Guideline**; **Alternate** guidelines: (NCCN guidelines, Clin Infec Dis 2011;52:e56, J Oncol Pract 2018;14:250)
- **Empiric abx**: within 1h; up to 70% mortality if delayed abx (Antimicrob Agents Chemother 2014;58:3799)
  - **Gram-negatives (PsA dosing)**: broad Gram-negative coverage (including PsA) within 60min of presentation
    - **Cefepime 2g q8h** (or ceftazidime 2g q8h), pip/tazo 4.5g q6h, or meropenem 1g q8h
    - PCN allergy: confirm allergy; use Penicillin Hypersensitivity Pathway and test-dose cefepime or meropenem; consider allergy consult. If true allergy, use aztreonam (avoid in ceftazidime allergy) + levofloxacin
    - High-risk ESBL: meropenem 1g q8h (2g q8h if meningitis)
    - Low risk: IV -> PO regimen (discuss w/ attending); cipro/levoflox + amox-clav vs clinda (if PCN allergy); avoid if prior FQ ppx
  - **Gram-positives**: **NOT part of FN empiric regimen** (JAC 2005;55:436; Clin Infect Dis 2011;52:56)
    - Indications: HoTN/severe sepsis, GPC bacteremia, catheter-related infxn (rigors with infusion, erythema on exam), SSTI, PNA on imaging, MRSA colonization (esp in HCT), severe mucositis + prior FQ ppx + GNR coverage with ceftaz
    - First line: vanc; if there is concern for VRE then daptomycin (unless pulmonary process, inactivated by surfactant) or linezolid
  - **Anaerobes**:
    - Indications: intra-abd source, C. diff, oral ulcer/periodontal infxn, post-obstructive PNA, necrotizing ulceration
  - **Fungi**:
    - Indications: **F&N >4-7d** despite abx, ⊕ fungal biomarkers, ⊕ CT chest (circumscribed, air crescent, cavity), ⊕ BAL Cx
    - Micafungin 100mg q24h or Amphotericin 5mg/kg q24h (admin after 500cc NS)
- **Modification/duration**: Note recommended duration of empiric therapy varies between guidelines (Ther Adv Infect Dis 2022;9)
  - **Resolution of fever**:
    - Documented infxn: narrow abx and tx for recommended course, then switch to FQ ppx until ANC >500
    - Culture negative: continue empiric treatment until afebrile & ANC >500 vs narrow to FQ ppx if afebrile x4-5d
  - **Fever continues >4-7d**:
    - Clinically stable: do not broaden abx or add vanc, consider other causes (e.g. engraftment, differentiation, GVHD, TLS, drug fever, thrombophlebitis, hematoma, hepatosplenic candidiasis), discuss w/ ID
    - Clinically worsening: broaden abx ± fungal coverage, consider CT chest ± bronch to evaluate for fungal infxn
  - **Catheter-associated infection**: also see *Bloodstream Infections & Endocarditis*
    - Coag-negative staph, non-VRE Enterococcus: can keep line if IV abx + abx lock x2w
    - Staph aureus, PsA, fungi: must remove line. For gram negative, d/w ID/attending, consider line removal vs. lock therapy
    - Complicated infxn: (endocarditis, septic thrombosis, bacteremia/fungemia >72h post removal), remove line, abx x4-6w
- **Prophylaxis**:
  - **Anti-microbial ppx**: refer to NCCN guidelines for more specific indications, also see *Hematopoietic Cell Transplantation*
    - Antibacterial (FQs): high-risk pts (heme malignancy) and attending discretion for intermediate-risk pts
    - Antifungal (azole vs echinocandin): select heme malignancies during neutropenia and early post-HCT
    - PJP (TMP-SMX, atovaquone): if ≥20mg prednisone daily for ≥1mo, purine analog, CD4≤200, or post-HCT/CAR-T
    - HSV/VZV (acyclovir vs famciclovir): heme malignancy on therapy, post-CAR T, or post-HCT (1-2 years)
  - **G-CSF**: ppx reduces incidence and duration of FN when risk >20% but does NOT decrease mortality (JCO 2015;33:3199); consider adding if critically ill, anticipated prolonged neutropenia, PTLD, or HIV. Caution if leukemia (d/w attending)

Oncology Inpatient Leukemia & Lymphoma Regimens

Regimen*	Protocol	Supportive Care
Leukemia		
7 + 3 7d of **cytarabine** and 3d of **anthracycline** (Idarubicin or Daunorubicin)	**Induction for AML** Idarubicin 12 mg/m2 daily x3days Daunorubicin 60-90 mg/m2 daily x3 days Cytarabine 100-200 mg/m2 continuously, days 1- 7	**Premedication:** Assess EF prior given cardiotoxicity risk. Vesicant. **Emetic Risk:** High **Neutropenia Risk**: High **Growth Factor:** Filgrastim or Pegfilgrastim
Decitabine (5-aza-2'-deoxycytidine, Dacogen) 28-day or 42-day cycle until disease progression or toxicity	**MDS/AML:** 20 mg/m^2 IV over 60 min daily on Days 1-5 **AML with unfavorable cytogenetic and/or *TP53* mutation:** 20 mg/m^2 IV over 60 min daily on Days 1-10	**Premedication:** PPx or tx symptoms with bowel regimen, antidiarrheals, IVF and/or electrolyte replacement **Emetic Risk:** Minimal-to-low; PRN for breakthrough **Neutropenia Risk**: Moderate **Growth Factor:** Filgrastim or Pegfilgrastim
5-Azacytidine (5-Aza, Azactidine, Vidaza, Azadine, Onureg) 28-day cycle until disease progression or toxicity	**AML:** 300mg PO qday on D1-14 **MDS:** Cycle 1: 75mg/m^2/day for D1-7; Subsequent Cycles: 75 mg/m^2/day q4weeks (Dose may be increased to 100 mg/m^2/day if no benefit after 2 cycles)	**Premedication:** During first 2 PO cycles, administer an antiemetic 30 min prior to each dose; antiemetic ppx may be omitted after 2 cycles if no n/v **Emetic Risk:** Moderate, Cycle 1-2 **Neutropenia Risk**: Moderate **Growth Factor:** Filgrastim or Pegfilgrastim
HiDAC (High-Dose ara-C) **(ara-C, Cytarabine)**	**Consolidation:** **HiDAC:** 1.5-3 g/m^2 over 3h q12h on Day 1, 3, 5 -OR- Day 1, 2, 3 for 3-4 cycles	**Premedication:** Corticosteroid eye drops throughout consolidation **Emetic Risk:** Moderate **Neutropenia Risk**: Moderate **Growth Factor:** Filgrastim or Pegfilgrastim
Hyper-CVAD <u>Dose-intensive phase:</u> 8 cycles of Hyper-CVAD alternating with High-Dose Methotrexate and Cytarabine (HD MTX-ara-C) + intrathecal (IT) PPx each cycle for 16 IT treatments. <u>Maintenance phase:</u> Dependent upon clinical response	**Hyperfractionated Cyclophosphamide (CP):** 300 mg/m^2 IV over 3h q12h for 6 doses on days 1-3, given <u>with</u> Mesna 600 mg/m^2 as continuous infusion ending 6h after last dose **Vincristine:** 2 mg IV Days 4 and 11 **Doxorubicin:** 50 mg/m^2 IV on Day 4 **Dexamethasone:** 40 mg daily on Days 1-4; 11-14 **HD MTX-ara-C:** **MTX:** 200 mg/m^2 IV over 2h followed by 800 mg/m^2 IV over 24h on Day 1; Leucovorin rescue starting 24h after completion MTX; dose according to MTX level **ara-C:** 3 g/m^2 over 2h q12h x 4 on Days 2-3 **Methylprednisolone:** 50 mg IV twice daily Days 1-3 **CNS PPx:** *Risk-stratified CNS ppx with alternating intrathecal (IT) high-dose methotrexate (MTX) and cytarabine (Ara-C)* **MTX:** 12 mg IT on Day 2 **ara-C:** 100 mg IT on Day 8	**Premedication:** NS 100mL/hr prior to chemotherapy. Continue through cyclophosphamide **Emetic Risk:** Day 1-5, high **Neutropenia Risk**: High; Median times to granulocyte and platelet recovery were 18 and 21 days, respectively **Growth Factor:** Filgrastim or Pegfilgrastim on Day 5 (24h after chemotherapy)
ATRA/ATO <u>Induction:</u> ATRA should be continued until CR is achieved. Restage with BM aspirate and biopsy on Day 28	**Induction:** **All-Trans Retinoic Acid (ATRA):** 45 mg/m^2 in divided doses daily, starting Day 1. S*tart ATRA upon first suspicion of APL* **Arsenic trioxide (ATO):** 0.15 mg/kg IV daily, starting after cytogenetics confirmation **Consolidation:** **ATRA:** 45 mg/m^2/d for 2 weeks q4weeks for a total of 7 cycles **ATO:** 0.15 mg/kg IV 5d/wk for 4 weeks q8weeks for a total of 4 cycles	**Premedication:** none **Emetic Risk:** Moderate **Neutropenia Risk**: High **Differentiation Syndrome:** maintain a high index of suspicion (fever; WBC >10k; SOB; hypoxemia; pleural or pericardial effusions). Discuss steroid use with attending, supportive **Growth Factor:** Myeloid growth factors should not be used during induction. May be considered during consolidation for life-threatening infection, sepsis, *etc*.
Hydroxyurea (Hydrea; HU)	**HU:** Starting dose 500 mg BID or 1000 mg QD; dose adjusted to ANC 500-1000; cytoreduction and WBC count goal based on disease and therapy regimen	**Premedication:** none **Emetic Risk:** Minimal-to-low **Neutropenia Risk**: Moderate **Growth Factor:** count recovery within days of stopping agent

Lymphoma		
R-CHOP 14-day cycle, restage after 2-4 cycles, total 3-6 cycles +/- radiation	**Rituximab**: 375 mg/m² IV Day 1 **Cyclophosphamide**: 750 mg/m² IV over 30 min Day 1, combined oral and IV hydration 2-3L on day of chemo **Doxorubicin**: 50 mg/m² IV Day 1 **Vincristine**: 1.4 mg/m² (max 2 mg) IV over 15-20 min Day 1 **Prednisone**: 100 mg PO Days 1-5 **CNS PPx:** 4-8 doses of IT MTX and/or cytarabine or high-dose MTX during the course of treatment	**Premedication:** Diphenhydramine and acetaminophen prior to rituximab **Emetic Risk:** Day 1, high **Neutropenia Risk**: High **Growth Factor:** Filgrastim or Pegfilgrastim on Day 6 or 3-4 days after completion of chemotherapy until count recovery
Dose-Adjusted R-EPOCH 21-day cycle, 6 cycles (dose adjustments based on ANC counts from BID CBC during previous cycle)	**Rituximab**: 375 mg/m² IV Day 1 **Etoposide:** 50 mg/m² infusion over 24h daily on Days 1-4 **Doxorubicin:** 10 mg/m² continuous infusion over 24h daily on Days 1-4 **Vincristine:** 0.4 mg/m² continuous infusion over 24h daily on Days 1-4 **Cyclophosphamide:** 750 mg/m² IV over 30 min Day 5, combined oral and IV hydration 2-3L on day of chemo **Prednisone**: 60 mg PO BID Days 1-5 **CNS PPx:** 4-8 doses of IT MTX and/or cytarabine or high-dose MTX during the course of treatment	**Premedication:** Diphenhydramine and acetaminophen prior to rituximab **Emetic Risk:** Days 1-5, high **Neutropenia Risk**: High **Growth Factor:** Filgrastim or Pegfilgrastim after completion of chemotherapy until count recovery
R-ICE 14-day cycle, 3 cycles	**Rituximab**: 375 mg/m² IV Day 1 **Ifosfamide:** 5,000 mg/m² IV continuous infusion over 24h on Day 2 with NS at 1.5-3 ml/kg/hr beginning 2h prior and ending 2-4h after infusion **Mesna:** 5,000 mg/m² IV infusion over 24h on Day 2 **Carboplatin:** Dose ~ AUC 5 mg/mL IV over 30 min on Day 2 **Etoposide:** 100 mg/m² daily on Days 1-3	**Premedication:** Diphenhydramine and acetaminophen prior to rituximab **Emetic Risk:** Day 1, 3 – Low; Day 2 High **Neutropenia Risk:** High **Growth Factor:** Filgrastim or Pegfilgrastim on Day 4 or 3-4 days after completion of chemotherapy until count recovery
ICE	See **R-ICE** above, hold rituximab	
R-DHAOx 21-day cycle	**Rituximab:** 375 mg/m² IV Day 1 **Dexamethasone:** 40 mg PO daily on Days 1-4 **Cytarabine:** 2,000 mg/m² IV Day 2 (2 doses) **Oxaliplatin:** 130 mg/m² IV over 2h on Day 1	**Premedication:** Diphenhydramine and acetaminophen prior to rituximab **Emetic Risk:** Moderate **Neutropenia Risk:** High **Growth Factor:** Filgrastim or Pegfilgrastim on Day 5 or 3-4 days after completion of chemotherapy until count recovery
R-Bendamustine 28-day cycle, 6 cycles	**Rituximab:** 375 mg/m² IV Day 1 **Bendamustine:** 90 mg/m² IV over 10 min **or** IV over 30 min daily on Days 1-2, CVC recommended for administration	**Premedication:** Diphenhydramine and acetaminophen prior to rituximab **Emetic Risk:** Moderate, Day 1-2 **Neutropenia Risk**: High
High-dose Methotrexate (MTX) Dependent on chemotherapy regimen and count-recovery for 1-8 cycles	**CNS PPx:** **MTX:** 3,000-3,500 mg/m² over 4h on Day 1 on alternate days of chemotherapy regimen **Leucovorin:** 25 mg IV over 15 min **or** PO on Day 2 starting 24h from initiation of MTX and q6h until MTX < 0.05 uM	**Hydration:** Alkaline hydration with 5% Dextrose in sodium bicarbonate 100 mEq/L at 150 cc/hr 4h prior until 72h after completion of MTX infusion **Emetic Risk**: Days of MTX, moderate **Neutropenia Risk:** High **Growth Factor:** Filgrastim or Pegfilgrastim on Day 4 or 3-4 days after completion of chemotherapy until count recovery
Solid		
FOLFOX, FOLFIRI, FOLFOXIRI, FOLFIRINOX (FOL) Folinic Acid 1d (F) 5-Fluorouracil 1-2d (IRI) Irinotecan (OX) Oxaliplatin 1d	**Folinic Acid:** 200 mg/m² IV Day 1 **Oxaliplatin**: 85 mg/m² IV Day 1 **Irinotecan** 180mg/m² IV Day 1 **Fluorouracil**: 400 mg/m² IV bolus followed by 2400 mg/m² for 2 days	**Toxicities:** If acute cholinergic syndrome appears use atropine. Can also have laryngospasm and rarely, coronary artery vasospasm spasm. **Emetic Risk:** High **Neutropenia Risk**: High **Growth Factor:** Filgrastim or Pegfilgrastim on Day 6 or 3-4 days after completion of chemotherapy until count recovery

*Chemo regimens may be modified based on genetics, risk stratification level, cardiac history, QTc prolongation. For further details on stratification and protocol details see **NCCN.org**

Geriatrics & Palliative Care — Pain Management

General Approach to Pain Management (NEJM 2015;373:2549; Lancet 2011;377:2236; Fast Facts app for pearls)

- A comprehensive pain hx is essential to guiding therapy. Goal is to maximize level of functioning and quality of life.
- Step-wise approach to pain management: (WHO Guidelines; CDC guidelines; DFCI Pink Book)
  - Mild to moderate pain: non-opioids and adjuvants
    - Acetaminophen: max dose 4g daily, 2-3g safe in liver disease (Br J Clin Pharmacol. 2016;81:210)
    - NSAIDs: celecoxib best if ↑GIB risk, ketorolac if severe pain [10 –15 mg recommended, no added analgesia with higher doses (Am Fam Phys 2017;96:262)], use with caution in CAD, renal disease, IBD
  - Moderate to severe pain: schedule non-opioid options, try topicals, then consider short-acting opioids PRN
  - Severe pain: requiring round-the-clock opioids. Discuss w/ attending, consider adding extended release (ER) meds
    - Avoid ER opioids if pain source is expected to resolve (e.g., bone fracture, hematoma, abscess, post-procedural)
- "Basal-bolus" strategy: Obtain basal level of pain control throughout the day with scheduled oral doses + PRNs for breakthrough pain

Pain Archetypes and Useful Adjuvant Analgesics

- Somatic/musculoskeletal: easily localized, sharp, aching, gnawing
  - Bony pain: high dose NSAIDs or steroids*. Consider palliative XRT (if cancer-related) or surgery
  - Muscle spasm: topical lidocaine, capsaicin, methyl salicylate-menthol ointment; muscle relaxants (cyclobenzaprine, baclofen, tizanidine; *watch for sedation & delirium*)
- Visceral: deep tissues and internal organs, vague, referred or difficult to localize
  - Visceral distension (e.g., hepatic capsular stretch from liver mets, malignant bowel obstruction): depends on etiology but steroids* can be helpful. Can consider plexus block with Chronic Pain
- Inflammatory: associated with other signs of inflammation (swelling, erythema, warmth)
  - NSAIDs (systemic or topical), steroids*
- Neuropathic: burning, stinging, allodynia, hyperalgesia
  - Topical: capsaicin, camphor/menthol, lidocaine, diclofenac gel. POs in chart below (start low & go slow in older adults)
- Non-pharmacologics: PT/exercise/activity, heat or ice, CBT, treating comorbid psych dx, massage, acupuncture, other integrative therapies (note: for inpatient, massage and acupuncture currently only available for heme/onc patients)

*Considerations with steroids: in cancer patients, may interfere with treatment (e.g immunotherapy) and/or diagnostics. If prolonged course, will need GI and PJP ppx; determine who will manage taper plan at discharge

Neuropathic Pain and Opioid-Sparing Analgesia (*R – dose adjustment needed for renal function)

Drug	Initial Dose	Titration	Dose range	Notes
Gabapentin	100 mg po TID *R	Inc 100 mg tid q3 days	300 – 3600mg/day	Dose adjust for renal function; may take a few weeks to see effect
Pregabalin	75 mg BID or 50 mg TID *R	Can inc by 50-150mg/day within 1 wk if tolerating	300 mg / day in 2-3 divided doses	
Duloxetine	20 mg daily *R	Inc by 20-30 mg per week	20-60 mg / day	Common side effect sweating (6%); avoid if CrCl<30ml/min
Venlafaxine	37.5-75mg daily *R	Inc by 75 mg q 4 days	75 – 225 mg /day	Allow 4-6 wks for effect; Risk of withdrawal syndrome when stopped (need taper)
Amitriptyline / **Nortriptyline**	25 mg at bedtime, 10 mg in frail/elderly	Titrate dose every few days	25-100 mg at bedtime	Allow 2-4 wks for effect; Less side effects with nortriptyline

Ketamine (General Guidelines on Ketamine for Acute Pain, MGH Ketamine Use Policy)

Initiation of ketamine, and adjustment of dose requires consultation with either **Palliative Care or Chronic Pain Service**

- **Consider in:** 1) Expected severe post-operative pain (abdominal/thoracic surgery, orthopedic surgeries) 2) Opioid tolerant pts presenting for surgery or acute pain exacerbations. 3) Pts at increased risk of opioid-related respiratory depression (OSA)
- **Adverse effects**: rare at sub-anesthetic dosing (HTN, tachycardia, arrythmia, hallucinations, increased ICP, increased bronchial secretions, N/V). Psychomimetic effects may be treated w/ 0.5-1 mg IV haloperidol or 1-2 mg IV lorazepam.
- **Avoid in**: poorly controlled cardiac disease, pregnancy, active psychosis/hospitalization hx (<3 yrs), severe liver dz, elevated ICP/IOP

Opioids (CDC app for guidelines & MME calculator)

- Opioid-tolerant defined as total daily dose (TDD) x7d: morphine 60mg/oxycodone 30mg/hydromorphone 8mg/fentanyl 25mcg/h
- Patients on buprenorphine/methadone for OUD, or active non-Rx OUD → treat pain w/ full agonists if needed, See *OUD & Withdrawal* for strategies for each scenario. Can consult ACT if needed for assistance.
- Avoid using combo pills (limits titration flexibility). See Opioid Pharmacokinetics Chart for sample initial dosing.

Opioid Pharmacokinetics Chart

* For opioid naïve patients in moderate or severe pain. If opioid tolerant, consider home PO breakthrough dose or 10-20% of ER dose
**If concern for hepatic or renal metabolism, would use wider dosing intervals and be more cautious with uptitration

	Route	Sample Initial PRN Doses* (dose reduce ~50% for elderly)	Onset (min)	Peak Effect (min)	Duration of Effect (hr)	Clearance/Metabolites**
Morphine	IV	2-4mg q3-4h prn	5-10	10-30	3-5	AVOID in renal disease
	PO	7.5-15mg q3-4h prn	15-60	90-120	4	
HYDROmorphone	IV	0.2-0.4mg q3-4h prn	5-20	15-30	3-4	Safer in renal and liver disease
	PO	2-4mg q3-4h prn	15-30	90-120	4-6	
OxyCODONE	PO	5-10mg q3-4h prn	15-30	30-60	4-6	2nd line for renal disease

FentaNYL	IV	25-50mcg q15-30m prn	<1	5-7	45m to 2+ hr	Safer in renal and liver disease
Methadone	IV	*Consult pain and/or pall care*	10-20	60-120	4-6	Safer in renal and liver disease
	PO		30-60	90-120	4-12	

Methadone:* Beneficial in neuropathic pain (TID dosing for pain)
- Cannot be converted linearly from other opioids
- Safety concerns: bimodal short and long half-life (up to 150 hours), QTc prolongation (monitor K, Mg)
- Takes days to reach steady state. Titrate q4-5 days

Fentanyl Patch:* Safer in both liver and renal dysfunction
- Safety concerns: if febrile, dose reduce or remove patch (cutaneous vasodilation → faster transdermal absorption)
- Less effective in cachexia (less subq fat for absorption)
- Requires 18-24h to reach therapeutic level

*Initiate with Chronic Pain/Palliative Care consult. Must ensure that there is an outpatient prescriber at discharge (PCP or subspecialist).

Opioid Uptitration/Rotation

- If pain only moderately controlled with scheduled doses (not in pain crisis, no side effects), ↑ total daily dose by 30-50%
- If taking ER opioid and needing >3-4 rescue doses daily, ↑ ER dose by 50-100% of total rescue dose used in past 24h
- Rotate opioids if side effects, dose reduce by 25-50% when rotating. See example/table below.
- If pain persists, repeat pain hx, consider total pain, and involve an interdisciplinary team (eg, palliative care, chronic pain, etc)

Ex: Pt takes morphine ER 60mg PO q12h +/- morphine IR 15mg PO BID
Step 1) Calculate total daily opioid requirement
TDD = (60mg x 2 doses) + (15mg x 2 doses) = 150mg morphine
Step 2) Convert TDD to equivalent dose of new opioid

$$\frac{30\text{mg morphine}}{20\text{mg oxycodone}} = \frac{150\text{mg morphine}}{x} \quad x = 100\text{mg oxycodone}$$

Step 3) Reduce dose by 25-50% to account for incomplete cross-tolerance → ~60mg oxycodone total daily dose
Step 4) Divide TDD by number of doses per day
- If initiating or converting to long-acting opioid, divide TDD into ER doses and add breakthrough dose (10-20% of TDD of ER opioid)
Final dose: oxycodone ER 30 mg q12h with 10 mg oxycodone q4h prn

Opioid Equianalgesic Doses		
Drug	**PO (mg)**	**IV (mg)**
Morphine	30	10
OxyCODONE	20	n/a
HYDROcodone	20	n/a
HYDROmorphone	7.5	1.5
FentaNYL*	n/a	0.1 (100 mcg)
Fentanyl patch (mcg/hr)	**Morphine PO (mg/day)**	
25	50	

*Caution w/ conversion to fentanyl (short duration of action)

Pain Crisis Management

Severe worsening of pain; while treating, pursue reasonable diagnostic workup for etiology (e.g., bowel perforation/peritonitis, procedural complication, bleeding). **Goal is reduction in pain score by at least 50%**. In sickle cell VOE, **follow patient's guidance**/Acute Care Plan

1) Opioid-naïve: give morphine IV 2-5mg or hydromorphone IV 0.2-0.4mg bolus dose
   Opioid-tolerant: convert usual breakthrough PO dose or 10-20% of total daily ER dose to IV and administer
2) Assess for response after 15min:
   - No pain relief and no side effects → increase dose by 50-100%
   - Minimal relief and no side effects (<50% reduction in pain score) → repeat the same dose
   - Pain reduced >50% and no side effects → reassess in 2-3h, use this dose as new breakthrough dose
   - Side effects with no pain relief → rotate to different IV opioid (no dose reduction if uncontrolled pain).

Patient-Controlled Analgesia (PCA)

- Appropriate for patients who are alert & oriented and able to use equipment. Families may NOT use PCA by proxy
- Requires daily delirium assessment (ie, CAM/4AT). Unrecognized delirium can obscure pain hx/medication use.
- Enables frequent administration of pain meds (vs max q1-2hr)
- Order "General PCA" (opioid-naïve pts) or "High Risk PCA" (BMI >40, hx OSA, RASS -2 to -5, age >65). If pt is opioid-tolerant, requires basal rate, consult Palliative Care/ Pain
- Increases in basal rate takes ~12 hrs to reach steady state: adjust basal rate q24hrs. If nighttime awakening w/ pain, can increase in basal rate at night

General Opioid-Naïve PCA Dosing		
	Morphine	**Hydromorphone**
Patient Administered Dose	1.5mg	0.2mg
Lockout Interval (per min)	10-15min	10-15min
One-Hour Dose Limit	6mg	1.4mg
RN/Clinician Bolus (for breakthrough)	2mg q30min PRN	0.3mg q20min PRN
Continuous Infusion Rate	0mg/hr	0mg/hr

Adverse Effects of Opioids and Management

- **Respiratory depression**: Follows sedative effects. Hold opioid, consider low dose naloxone but CAUTION if on high dose ER opioids
  - Dilute 0.4mg naloxone (1ml) in 9ml saline, give 1-2ml q2min until ↑RR or mental status improves. Naloxone half-life is 30-120min, watch for **recurrence** of resp depression and consider naloxone gtt. All patients d/c'd on opioids need a naloxone script
- **Constipation**: ALWAYS start **standing senna and/or Miralax** when initiating opioids; use other laxatives if needed; methylnaltrexone QOD if failed laxative therapy (but can cause severe nausea/cramping; avoid if concern for GI obstruction)
- Opioid-induced hyperalgesia: generally seen w/ high doses (or lower doses in CKD), consider rotating opioids and involving pall care
- Myoclonus: reduce dose or rotate opioid, increase hydration; can give low dose BZD, baclofen, or gabapentin. If persists, c/s pall care
- Nausea/vomiting: start prochlorperazine, metoclopramide, haloperidol, or low dose naloxone gtt; **avoid ondansetron** (constipating)
- Pruritus: mediated by mu receptor (not histamine – Benadryl ineffective unless rash/allergic reaction); consider opioid rotation, ondansetron, nalbuphine 5mg IV q6h, or low dose naloxone gtt
- Sedation: occurs prior to resp depression. Consider CNS stimulant (dextroamphetamine, methylphenidate although rarely prescribed)
- Delirium: reduce dose or rotate opioid; IV Haldol 1-2.5mg BID-QID or IV/PO Zyprexa 2.5-5mg PO QD-BID

Geriatrics & Palliative Care — Adv Care Planning & Code Status

SERIOUS ILLNESS CONVERSATIONS — MGH CONTINUUM PROJECT

When? Conversations can be planned or may happen spontaneously in any setting (NEJM 2014;370:2506). Should discuss early in disease course as outpatient, or:

- New, progressive (eg, increasing hospitalizations/ED visits, intolerance of guideline-directed therapies), or life-altering serious medical illness such as advanced cancer, ESRD, ESLD, HF, COPD
- Prognosis trigger: "Would I be surprised if this patient died in the next year?" (J Palliat Med 2010;13:837). Life expectancy <6mo (UCSF calculator, J Palliat Med 2012;15:175)
- Age >80 and hospitalized if no previous documentation; see *Geriatric Assessment & Frailty*

Why? Longitudinal SICs help explore illness understanding, hopes/worries, and what matters most. Involves pt-centered recommendation regarding a care plan that aligns with pt goals. Can be used for the purposes of Advanced Care Planning, discussion of transition to hospice/CMO, or referral to palliative care (more than just code status)

How?

Preparation for planned meetings:

- Consider a palliative care consult prior to the formal meeting if complex decisions/psychosocial issues/family conflict.
- Identify time and location to accommodate the patient and their loved ones, RN, SW, primary team, and consultants as applicable.
- **Pre-meet** with team, including consultants, to discuss: **goals, unified assessment of clinical scenario, if a clinical decision needs to be made urgently, and if so, what are treatment options and team recommendations (in alignment w/ pt stated goals)**

MGB Serious Illness Conversation (SIC Guide, Videos):

Step	Suggested Prompts
Open the conversation	"I'd like to talk about what is ahead with your health. Would that be ok?"
Assess prognostic awareness	"What is your understanding of your health?" "Looking to the future, what are your hopes about your health? What else?" "What are your worries? Tell me more."
Share worry	"Would it be ok if we talked more about what may lie ahead?" "I hear you're hoping for ____ and I worry the decline we've seen will continue" or "I worry something serious may happen in the next few wk/mth/yrs." "It can be difficult to predict what will happen with your health."
Align	"I wish we didn't have to worry about this"
Explore what's important	"What gives you strength as you think about the future of your health?" "If your health worsens, what is most important to you? "How much do your family or friends know about your priorities and wishes?"
Make a recommendation	"It sounds like ____ is very important to you." "Given what's important to you, I would recommend_____"

Document Serious Illness Conversation: (Refer to Advanced Care Planning Module in Epic)

- Patient ID banner (top left of storyboard): click "Code: ___" → "Advance Care Planning Activity" → "Serious Illness Conversation" in left tab; fill out SIC form " "Close"
- Open a note with type "Advance Care Planning" and use the dot phrase to insert the SIC → type .seriousillnesslast
- Consider filling out ACP forms if not already filled out (see Advanced Care Planning Forms)

ADVANCE CARE PLANNING FORMS

- **Health Care Proxy (HCP)/medical power of attorney**: an advance directive document that designates a healthcare agent to make future medical decisions if patient loses capacity. Expressly authorized in MA by statute. Filling out this form is a priority for all patients but more urgently for older adults, those with emerging cognitive impairment, and those with multimorbidity and/or complex life-limiting illnesses.
  - *If no HCP*: see Section 3, bullet 6 of MA: An Act Improving Medical Decision Making
- **Living Will**: an advance directive document in which a competent person specifies future medical treatments in the event of incapacity (usually at end-of-life or if in a persistent vegetative state). Can be used as evidence of a person's wishes, but not considered to have legal authority (no MA statute that expressly authorizes)
- **MOLST** (MA Medical Orders for Life-Sustaining Treatment; pink form available on all medical units): medical orders for patients with multimorbidity or serious illness that documents preferences for CPR, intubation, hospital transfer, artificial nutrition, dialysis, and more
  - Transferrable to outside facilities; must complete MOLST prior to discharge to rehab/SNF if patient DNR/DNI
  - Remember that you **do not** have to fill out or discuss everything on the back page (clinical discretion)
  - Remember that these decisions **can be changed** (fill out a new MOLST if decisions change)
- **Links to existing MOLST/HCP** forms are found in Advance Care Planning Activity tab or scanned into the Media tab
  - If filling out a new form, provide patients with a copy and scan into Epic for future documentation

CODE STATUS DISCUSSIONS

General Considerations

- Confirm directly with the patient/HCP, MOLST, and/or prior documentation by outpatient providers
- Readdress if a patient's clinical status changes, or if code status appears discordant with the clinical setting, Do **not** need to routinely readdress on admission if has been recently addressed by outpatient providers

- Code status ≠ ACP. Code status is a medical procedure for which harms/benefits should be weighed iso clinical context.
- Many procedural teams (i.e. cards, surgery) require temporary reversal of DNR/DNI periop, often 30d (JAGS 2022;70:3378-3389):
  - If changing code status pre-op (i.e. TAVR), **ensure your discharge documentation includes changing status back**/date of conditional code status end
  - If changing code status during early post-procedure or during chemotherapy, **notify procedural team/primary oncologist**

Survival Outcomes (Circulation 2019;139:e56)

- *Out-of-hospital cardiac arrest*: survival to hospital discharge 10.4%; survival with good neurologic function 9.9%
- *In-hospital cardiac arrest*: survival to discharge 25.6%; survival with good neurologic function 22%
  - Favorable prognostic factors: ACS, drug overdose, drug reaction (up to 40% survival)
  - Unfavorable factors: age >80 (<10% survival), multi-organ failure, sepsis, advanced cancer, ESRD, ESLD, dementia
  - Post-arrest complications: hypoxic-ischemic brain injury, rib fractures, pulmonary contusion, prolonged ICU care, acceleration of physical and cognitive frailty/disability

Code status options:

Full Code	The patient would want all resuscitative measures to be used
DNR/Ok to Intubate	The patient would not want cardiac resuscitation but would want to be intubated in the event of impending respiratory failure
DNR/DNI	In the event of a pulseless cardiac arrest or respiratory failure, the patient would not want cardiac resuscitation or intubation
DNR/DNI/LLST Comfort Measures	The patient would want their care team to orient care around comfort only, and care not oriented around comfort may be withdrawn while still treating the patient's symptoms
Do not offer "Full Code Except Do Not Intubate." Cardiopulmonary arrest requiring CPR nearly always necessitates intubation, and thus this is not an appropriate code status.	

Conducting Code Status Discussions (JAMA 2012;307:917)

- Suggested framing: "Resuscitation is a medical procedure we would perform if your heart were to stop and you died. What have you heard about resuscitation?"
- Many people would prefer a natural death. If you prefer a natural death then we would protect you from these procedures and ensure your comfort." Approaches to discussion of code status based on scenario (Indication and goal based on NEJM 2020;382:2450)
- Suggested opener: "Have you ever discussed CPR and intubation with your medical team? I want to make sure that I understand whatever decisions you've made regarding those two interventions."

Scenario/Indication	Approach/Goal	Example
The patient has a stable condition and is likely to benefit from CPR/Intubation	Make sure the patient does not strongly prefer to avoid these medical interventions	"Right now, if your heart were to stop, you would receive CPR. Is this consistent with your goals?"
The patient already has a preference to limit CPR and intubation that needs confirmation	Confirm an already established preference	"Your records show that you made an emergency plan with your outpatient doctor to focus on comfort and allow for a natural death. This means that we would not use chest compressions to start your heart or a use a breathing machine. Based on my medical assessment, I think we should continue this plan now. Does that sound right to you? We will do everything else we can to help you get through this."
The patient has an advancing illness, and it is unclear whether the benefits of CPR and intubation would outweigh the burdens (the decision depends heavily on the patient's values and goals)	Shared decision-making	"If an emergency were to occur and your heart were to stop, it is difficult to predict what would happen if you received CPR or a breathing tube. Recognizing this uncertainty, if your heart were to stop and you were to stop breathing, what would you want your medical team to know about what is important to you?" "Given what's important to you, I would recommend_____"
The patient is at risk for decompensation/death, unlikely to benefit from CPR and intubation	Informed Consent	**Introduce/assess:** If urgent: "I wish we were meeting under different circumstances." **Share information:** "Given all that's happened, I worry that your health has worsened. What are your thoughts about how things have been going?" (Discuss medical situation, share concerns using hopes/concerns) **Explore goals: "**Given where we are, what is most important to you?" **Make a recommendation:** -"I recommend we make a plan to help you meet your goals and avoid treatments that are unlikely to help." -"I recommend that if your heart and lungs were to stop working, we focus on your comfort. This means having treatments such as oxygen and medication. This also means we would not use CPR or a breathing machine. Does that sound right to you?"

Geriatrics & Palliative Care — End of Life & Pronouncement

Anticipated Inpatient Death

- Involve family, chaplaincy (available 24/7), social work services, longitudinal providers (e.g. PCP, subspecialists) in/during EOL care
- Ask about religious/cultural traditions, final wishes, and/or any specific preferences/experiences to keep in mind
- When passing off a patient who may pass away, prep "**Post-Mortem**" section under "Discharge as Deceased" Epic Tab (see below)
  - Consider asking families about autopsies in advance if/when appropriate
- Assess whether you will need to notify the medical examiner's office. Common reasons:
  - Any death associated with acute or chronic use of alcohol or drugs (including alcohol-related cirrhosis);
  - Death associated with diagnostic or therapeutic procedures;
  - Death by accidental/unintentional injury (including falls, fires), violence, suicide, or uncertain circumstances

Organ Donation

- Eligibility: IF family & medical team elect to discontinue medical support in any ventilated patient with a non-recoverable injury/condition, team should then complete a New England Donor Services e-referral form (see below) **prior** to any of the following:
  - Initiating therapeutic hypothermia, initiating brain death testing, transitioning from FULL to either DNR, DNE, or CMO status
- DO NOT broach topic of potential donation with family; NEDs is specifically trained for this and will coordinate consent & donation process which can take up to 24hrs
- Care prior to donation: maintaining organ viability during severe autonomic/inflammatory responses following severe neurologic injury. Key goals: MAP 60-110, normothermia, UOP 0.5-1.0cc/kg/hr, LTVV (CCM 2015;43:1291; NEJM 2004;351:2730; JAMA Surg 2014;149:969)
- OR Prep: Death paperwork must be done by declaring MD (prep in advance). After vent withdrawal (usually extubation in OR), MD/RN coordinate sx management until time of death, declare death based on irreversible cessation of circulatory/respiratory function

Withdrawing Ventilatory Support (palliative extubation, discontinuation of NIPPV)

- Prior to extubation, refer to MGH MICU Policy & ATS Guidelines (AJRCCM 2008;177:912). Review plan with the following people:
  - Family: ask if they want time privately w/ pt prior to extubation. Review expected signs of dying process (agonal breathing/'rattle' of pooled secretions, mottled extremities), expected timeline (usually min to hrs [Chest 2010;138:289]), and plan for sx control
  - RN: ensure adequate PRNs for air hunger/pain (IV opioids), anxiety (IV Haldol or benzos), and secretions (glycopyrrolate) are at bedside (see *Comfort Focused Care*); may need continuous infusions depending on requirements; can use CMO order set. Stop paralytics though can continue any prior sedative and/or opiate infusion(s) utilized for comfort while mechanically ventilated
  - RT: determine plan for immediate withdrawal vs down-titration of vent support
- Do not withhold appropriate sx management because of concern for hastening death or concern for increased sedation
  - *"The Rule of Double Effect"* (NEJM 1998;338:1389): focus on managing sx. If in doubt, ask for help
  - The goal is adequate pain, dyspnea, and anxiety relief; dose based on ongoing symptoms and prior dose effectiveness

Death Pronouncement

- **PRONOUNCEMENT:** Introduce yourself to the family, express condolences, and explain what you are doing
  - **FEEL** for pulse, **LISTEN** for heart/breath sounds (>60 sec), **SHINE** light to assess for absence of pupillary reflex, and **NOTE** time at the end of your exam which becomes official time of death (do **NOT** need to say out loud)

- **QUESTIONS FOR NEXT OF KIN:** (**Not HCP; Order:** Spouse > Children > Other Fam). In MA, HCP does not remain in effect after death, and legal NOK assumes responsibility for post-mortem decisions.
  - Would they like to be connected with MGH Decedent Affairs Office (new service; provide support re: final arrangements; connecting family with spiritual care, social services, bereavement groups, and even financial resources for burial)
  - Would they want an autopsy? (consent NOK in MA, **NOT** HCP)
  - If yes, ask about organ disposition (i.e. do they want MGH to retain organs for further testing, education, research?)
  - Are there any other family members whom they would like you to inform?
  - Is anyone else coming to view body prior to transport to morgue? (have 4hrs; can't see body at morgue but can at funeral home)
  - **What you can tell family:** body is kept at MGH morgue until the funeral home they select calls MGH and arranges for pickup. Family should select and contact funeral home directly (Decedent Affairs office can assist with this)

> **Autopsies** are **free** & do not delay funerals (can still have open casket). They help determine cause of death & can be instrumental in advancing research.

- **ONCE YOU LEAVE THE ROOM:**
  - **Notify ATTENDING and PCP** (Email acceptable if death was expected)
  - **Electronic Documentation:** No longer paper form,* now section under Epic Discharge Tab called Discharge as Deceased, similar to standard floor discharge navigator layout – **NOTE: items CAN be prepped & saved ahead of time;**
    - In **"Cause of Death"** section: don't write "cardiac arrest" or "respiratory arrest"; Fill out as many **underlying causes** as applicable - do not need to fill in ALL the lines but be as specific as possible. See CDC guide for examples.
    - Call **Medical Examiner** if necessary (see above *"Prior to Death"*); document first name of said staff member.
    - Click on **New England Donor Services** referral link: replaces initial screening phone call
      - Opens separate online tab within Epic with patient's demographic info prepopulated/filled in; will need to answer several additional questions (cause of death, vent hx, whether + for HIV/HBV/HCV, if active cancer & what type if so);
      - Will still need to subsequently call **NEDS** coordinator (800-446-6362) to confirm above referral outcome
    - Call **Admitting Office** (x6-3393) to inform them of death. Will ask cause/time of death, Med Examiner, NEDS info;
  - **Document a brief "note of patient death"**: SmartPhrase ".MGHDOMDEATHNOTE"
  - Complete short **discharge summary** within the Discharge as Deceased Navigator tab discussed above
  - **Debrief** process and death with team or Night Teach

  *NWH requires paper documentation

End of life care General Principles

- The focus of EOL care is to enhance patient's comfort, optimize symptom management, and ensure alignment with what matters most to patient. Code status change to DNR/DNI or CMO (Comfort Measures Only) is **not a requirement**.
  - Note that EOL is a medical state while code status reflects patient goals/values. If code status appears discordant with medical state, close communication among team members is essential for clear understanding of GOC.
  - EOL care should involve all members of the interdisciplinary team (clinicians, SW, chaplains) so that a patient's physical, emotional, social, and spiritual domains of care are adequately assessed and comfort maximized. Additionally, allowing time with family and respecting cultural and/or religious rituals if feasible is important.
  - Communicate expected signs of dying and time course to loved ones. **Any clinical provider** (MD, NP, RN, SW, chaplain) **can request an EOL visitation policy exception with RN leadership irrespective of code status** if passing is expected.
- Prepare paperwork and logistical planning as feasible prior to death (see *End of Life and Pronouncement*)

Best Supportive Care: Management Considerations in CMO

- Comfort-focused Care (also called Comfort Measures Only or CMO): Approach to care with the goal to maximize comfort. **Does not mean all treatments are stopped** (e.g., pts may benefit from thoracenteses, paracentesis, or venting G tube if within pt's goals)
- Lines/tubes: Maintain PIV access as possible, d/c central line if feasible.
- Supplemental O_2**:** Not shown to have benefit if not hypoxemic. Instead, offer fan therapy, HOB elevation, IV/PO opioids (Am J Hosp Palliat Care 2020;37:294)
- Foley: Can maintain for comfort; discuss w/ RN.
- Stop labs/routine VS unless it is helpful in managing comfort. Reassure loved ones that we can use RR, temp, & appearance as guide
- Medications: Continue meds contributing to patient comfort, those that will prevent uncomfortable events (e.g., rate control, diuretics, inhalers, nitrates, anticoagulation for stroke ppx, AEDs for seizure control), or that have a withdrawal syndrome (e.g., SSRIs).
- Tube feeds, TPN/PPN, IVF: Generally avoid; may cause volume overload without meaningful benefit (JCO 2013;31:111). Instead, encourage good mouth care and food/drink for comfort as able. Reassure loved ones that appetite/thirst declines at EOL (Fast Facts).
- Supportive Care Unit: 10 bed unit on Phillips 20 & 21 for patients with serious illness who have acute symptom management or goals of care needs. Care teams include palliative care attending, NP/MDs, SW, spiritual care, and specialized CM**. Transfer to SCU may be appropriate if pt symptoms are not well controlled despite aggressive management on the gen med floor, though beds are limited.**

Example PRN Orders: if questions or concerns, consult Palliative Care for support

*Always treat acute symptoms with boluses rather than changing drip rate. Drips effectively act as long-acting meds

**If uncontrolled acute symptoms despite IV bolus, can repeat after 20-30min at same dose or doubled dose and change PRN dose

	IV access	PO only (No IV access)
Analgesia/Dyspnea	Opioids: see *Pain Management*. Can dose more frequently (uptitrate dose q30 min PRN for uncontrolled air hunger/pain) at EOL when goal is for aggressive symptom management (discuss w/ RN). Dyspnea: Start with 2-5mg IV morphine equivalents for the opioid naive	
Secretions *Stop TF, lay on side, pharm trial, reassure fam	Glycopyrrolate 0.2-0.4mg IV/SC q4-6hrs PRN	Glycopyrrolate 1mg PO q4-6hrs PRN *or* atropine 1-2 drops SL q6hrs PRN (of note, atropine crosses BBB & may contribute to delirium)
Delirium, Anxiolysis	Haloperidol 0.5-1mg IV q4-6hrs PRN	Haloperidol 0.5 mg PO q4-6 hrs PRN *or* Olanzapine 2.5-5mg SL q6h PRN
Anxiolysis associated with dyspnea	Lorazepam 0.5-1mg IV q4-6hrs PRN (increase as needed)	Lorazepam 0.5-1 mg PO q4-6hrs PRN (increase as needed)

Resources: Palliative Care Network of Wisconsin Fast Facts and app; DFCI resources: Pink Book for pain, Green Book for N/V

Hospice Overview

- Hospice: multidisciplinary care for patients with advanced illness and life expectancy <6mo with goal of providing best supportive care when disease modifying therapy is no longer effective. Paid through Hospice Insurance Benefit (most often through Medicare)
- **Can be provided in multiple locations,** including home (most common), SNF, hospice house, or acute care hospital depending on patient's care needs and caregiver support
- Services include intermittent nursing care (~1-2 visits/week with 24/7 on-call emergency support), social work, chaplaincy, all medications and supplies related to terminal illness or comfort, equipment (bed, commode, wheelchair etc.), home health aide, bereavement support, short-term respite care (provides relief for caregivers), and short-term inpatient care for symptoms that cannot be managed at home. **Caregiving most often provided by family and friends**
- **DOES NOT** cover room/board at facilities or 24/7 nursing care. More complex palliative or comfort interventions such as XRT, TPN, or advanced IV pain therapies (ketamine, lidocaine), are covered by hospices on a case by case basis.

General Inpatient Hospice (GIP)

- GIP Hospice: hospice level of care for pts who have short-term symptom mgt needs that cannot be provided adequately in any other setting (e.g., high flow O2, uncontrolled sx requiring IV medications, high RN needs for wound care/suctioning). Most appropriately offered at hospice house & this DC plan should be prioritized if pt can be transported.
- Consider GIP at MGH for pts who are actively or imminently dying and/or cannot safely transport. If admitted to GIP at MGH, pt will be "Discharged to Hospice" and Pall Care becomes primary team.
- Discuss w/ floor CM team (for insurance benefit screen and coordinate w/ hospice liaison), hospice agency (ie, Good Shepard, Care Dimensions, Norwell Home Health & Hospice), and Pall Care if pt is appropriate for GIP Hospice and, if so, which location

Geriatrics & Palliative Care — Geriatric Assessment & Frailty

GENERAL APPROACH TO THE COMPREHENSIVE GERIATRIC ASSESSMENT

- Overview: The comprehensive geriatric assessment (CGA) systematically identifies medical and psychosocial factors that lead to functional limitations for older adults and should be approached by an interprofessional team. One widely accepted framework is the "Geriatric 5Ms" (mind, mobility, medications, matters most, multicomplexity) (JAGS 2017;9:2115).
- Outcomes: CGA associated with increased likelihood that inpatients will be alive and in their own homes 3-12 months following discharge (Cochrane 2017;9:CD006211) & predicts operative/procedural risk (JAGS 2020;68(6):1235; EJSO 2016;42:1890-7). Outpatient, serial CGA provides opportunity to tailor care to the evolving needs of patients (JAH 2021;33:469).

Topic	Examples	Tools
Mind	Vision, hearing, mood, sleep, memory	PHQ-2 or Geriatric Depression Scale (English, Spanish) *Cognitive Tests (suggested stepwise approach):* 1. Mini-Cog (English, non-English languages) 2. RUDAS (minimizes effects of educational level, cultural learning, and language in assessing cog fxn) 3. MOCA (English, Spanish)
Mobility	Pain, feet, falls/fear of falling	Timed up and go test (<12s) Gait speed test (4m/5sec = 0.8m/sec) 30 sec Chair-to-Stand test (>8 in 30 sec)
Medications	High risk meds, polypharmacy, immunizations	See *Frailty & Polypharmacy*
Matters most	Social history, HCP, code status	Massachusetts HCP Resources for patients: Prepare for your care (5-step program for patients), The Conversation Project See *ACP & Code Status* for further info
Functionality	Appetitie/nutrition/weight Dentition/swallowing Constipation/incontinence Sexual history Substance use ADLs: bathing, dressing, toileting, transferring, feeding, etc iADLs: cleaning, finances, engaging w/ technology, etc	Mini-Nutritional Assessment (English, Spanish) Home Safety Assessment

Effective interventions to reduce falls:

- Home safety assessments: referral to PT/OT should explicitly request fall reduction program as well as home safety evaluation
- Repair of single cataract decreased risk of hip fracture in the year following repair (refer pts for of ophthalmologic exams)
- Discourage use of progressive lenses (older adults often less able to adjust to changes in depth perception with these lenses)
- Assess for orthostatic hypotension and completing comprehensive medication review. *See Polypharmacy*
- Multicomponent exercise programs (strength/resistance training, aerobic, & balance) done in groups superior to programs done alone
- Sit-to-stand repetitions both while hospitalized and at home

FRAILTY

Frailty is an identifiable clinical state in which an individual is more vulnerable to stressors due to reduced physiologic reserves. This increased vulnerability leads to increased risk of falls, hospitalization, loss of independence, iatrogenic harm and death from otherwise minor illnesses or low burden interventions (JAMDA 2013;14:392). ***Reframe "failure to thrive" as frailty.***

- Frailty is a geriatric syndrome. Though older age is risk factor but is not necessary/sufficient for the dx
- Frailty is ***dynamic***: individuals can move between different states of frailty over time.
- Frailty is ***potentially reversible***: modifying RFs can improve QoL and reduce morbidity and mortality (JAGS 2007;55:11)
  - Frailty Tools (In Epic: Rarely Used →Additional Tools→Geriatrics→Frailty Index) are most commonly based on:
  - ***Fried Frailty Phenotype Model***: physical manifestations of reduced physical reserves (self-reported exhaustion, unintended weight loss, low grip strength/weakness, slow walking speed, physical inactivity) (J Geront 2001;56:M146; BMC Geriatr 2013;13:64).
  - ***Rockwood Deficit Accumulation Model***: a concept in which 30 or more factors from the 5M domains and/or variables known to diminish over time is used to construct a Frailty Index (J Geront 2007;67:722).
  - Refer to Comprehensive Geriatric Assessment-Frailty Index or FRAIL screen (J Nutr Health Aging 2012;16:601)

Interventions for frailty (Age Ageing 2017;46:383)

- Screen for and treat high-risk comorbidities (e.g. urinary incontinence, osteoporosis, vision/hearing impairment, driving risk)
- Establish **patient- and family-centered goals** to guide treatment plan
- Exercise: PT; exercise programs (e.g. Tai Chi) can reduce fall risk (JAMA 2018;319:1705; BMC Geriatr 2020;20;108)
- Consults: for complex patients, refer for nutrition assessment for weight loss and/or concern for micronutrient deficiencies; out-patient Geriatric Clinic for follow-up CGA and longitudinal consultative geriatric care; MGB Home-Based Palliative Care for severe frailty and limited life expectancy.
- Cognition: inpatient: cognition screening,delirium precautions (limiting overnight VS/interventions, labs, lines/tethers, physical/chemical restraints); outpatient: OTand/or SLP consult (cognitive training, info processing, problem-solving, driving eval)
- Environment Modifications: consider SW consult, PT/OT consult, iCMP referral, Home Health (includes PT, OT, Speech, & SW)
- Address advanced directives/HCP/Code Status

Geriatrics & Palliative Care — Polypharmacy & Elder Abuse

POLYPHARMACY: PRESCRIBING AND DEPRESCRIBING MEDICATIONS

Medication Reconciliation: confirm meds w/ pt & family; ask about medication administration system (eg, blister packs, pill boxes)

- Review prior notes, d/c summaries, & paperwork from SNFs for med changes
- Look up pharmacy dispenses in Epic: Chart Review → Misc Reports → Medication Dispense History; or
- Call 24/7 pharmacies: CVS 781-391-2668 (dial 1, 2, "staff"); Walgreens 781-321-1765 (dial 2, #, "other question")
- Ask about OTC meds, herbal/dietary supplements (including CBD/THC), which can be easily missed culprits of drug-drug interactions
- Coordinate discharge Rx planning and education with patient, pharmacy, PCP.lower risk of readmission with intensive pharmacist intervention (med rec and education) and coordination with PCP (JAMA IM 2018;178:375), MGH Home Health

Deprescribing Medications:

- **Use tools** like Medication Appropriateness Index; MedStopper; deprescribing.org (include taper plans & info for patients/families)
- **Confirm eGFR with cystatin C:** Creatinine-derived eGFR can often overestimate CrCl in older adults due to sarcopenia
  - Renal adjustment of medications important for mitigating side-effects/complications (enoxaparin, apixaban, rivaroxaban, dabigatran, antibiotics, antiepileptics)
- **Classes to AVOID in geriatric patients**: See Beer's list (J Am Geri Soc 2019;67:674) and STOPP-START for further details
  - Anticholinergics: delirium, falls, blurred vision, urinary retention, tachycardia. Avoid antihistamines, TCAs, MAOIs, antimuscarinics (oxybutynin), muscle relaxants (cyclobenzaprine), prochlorperazine. *Long term use linked to increased risk for dementia* (JAMA IM 2015;175:401)
    - Anticholinergic Risk Scale: additive effect of multiple meds w/ minor anticholinergic effects can be significant.
  - Benzodiazepines: delirium, falls, cognitive impairment, etc. (also risk w/ non-BZD hypnotics e.g. zolpidem)
  - Antipsychotics: #mortality with antipsychotics in the elderly with underlying cognitive impairment (JAMA Psych 2015;72:438)
  - Peripheral alpha blockers and central alpha-agonists: -zosins and clonidine " risk of orthostasis and falls
  - Long-acting sulfonylureas and rapid/short acting insulin: hypoglycemia (do NOT use nighttime SSI in older adults)
  - PPIs: *C. diff*, bone loss/fracture (taper off or switch to H2 blockers unless clear indication for PPI)
  - NSAIDs: CVD, GI bleed, AKI (especially in elderly patients with decreased CrCl)
  - Aspirin for primary CVD prevention: bleeding (use with caution and reevaluate at age >70) (NEJM 2018;379:1509)
  - Tramadol: multiple drug interactions and receptor activity
  - Serotonergic medications: serotonin syndrome can present as anxiety or agitation w/ initiation or titration of meds in older adults
  - Parkinson's disease: ondansetron is antiemetic of choice. **Avoid** antipsychotics, metoclopramide, prochlorperazine

COMMON SIGNS OF ELDER ABUSE

- Generally includes persons 60 years or older (although this definition is state-dependent).
- Definition (CDC): "An intentional act or failure to act by a caregiver or another person in a relationship involving an expectation of trust that causes or creates a risk of harm to an older adult."
- Includes physical, emotional, sexual, neglect, abandonment, and/or financial abuse. Can present as:
  - Withdrawn affect, deferring to others to answer
  - Unwashed hair, dirty clothes, appearing unkempt (don't forget to look at feet and nails!)
  - Unclean or unsafe living conditions, mismatch in level of social supports/services vs needs based on physical or cognitive disability, tension w/ family around financial planning to help with care needs
  - Worsening of pressure ulcers, skin tears, weight loss
  - Lack of necessary medical aids (walkers/canes, adult-pull ups)
  - Unpaid bills, eviction notices, inability to hire more services/help or transition to a new level of care etc. despite adequate financial resources
- Risk Factors (NCEA): advanced age, female sex, non-white race, disability, cognitive impairment
- Screening
  - AMA recommends regular screening but USPSTF did not identify sufficient evidence (Screening tools validated in various settings are available for use, consider using comprehensive geriatric assessment above)
  - Concerns should prompt cognitive testing, functional assessment, and obtaining collateral to screen for unrecognized dementia as an underlying cause of these signs and symptoms (See "*Dementia*")
- **Guardianship** (Gerontology 2007;47:591-603): legal process that gives a guardian permission to take care of and make decisions for an incapacitated adult who does not have a pre-designated HCP. Consider guardianship in situations where the patient does not have capacity regarding **high-risk decisions** and no HCP identified. Pt may be determined to lack **competence** (legal status) by a court.
  - **If concern for abuse/neglect from HCP, obtain collateral from longitudinal providers and consider OCC consult before proceeding with guardianship process.**

REPORTING LOGISTICS

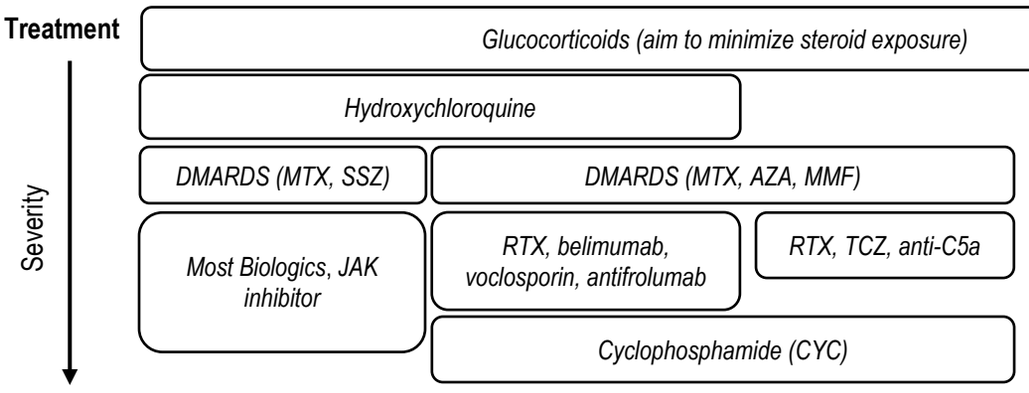
General, Caretaker, Facility

- Making a report through the Massachusetts Executive Office of Elder Affairs (can be made by any member of the healthcare team)
- Report can be made online or via phone: (800) 922-2275.
  - If you make a report via phone, must submit a mandated reporter form to the local Protective Services agency within 48h
  - To report abuse of a patient by nursing home or hospital staff, reach out to the other providers/institutions first to discuss and obtain collateral and understand greater clinical/social context. If continued concern, can contact the Massachusetts Department of Public Health: (800) 462-5540
- Similar to DCF reports, this is an ask to an objective, multi-disciplinary team to investigate concerns rather than a condemnation
- Documentation: No template currently available in Epic. Document findings as part of a progress note or in a separate encounter. Remember to be detailed but not inflammatory/derogatory in describing subjective & objective findings suggestive of abuse or neglect.

Rheumatology Approach to Rheumatologic Disease

OVERVIEW: rheumatologic diseases may be roughly separated into 4 categories

Category	Inflammatory Arthritis	Connective Tissue Disease	Vasculitis	Other
Major Diseases	RA, spondyloarthritis, crystalline arthritis, reactive arthritis	SLE, Sjögren's, scleroderma, MCTD, UCTD, myositis (DM, PM)	Small (GPA, MPA, EGPA, cryo, IgA), med (PAN), large (GCA, Takayasu), or variable vessel (Behcet's)	Autoinflammatory diseases, sarcoid, IgG4-related disease, VEXAS
Initial work-up	RF, anti-CCP, ANA, XRay	**ANA first.** Then: C3/C4, anti-Sm, anti-dsDNA, anti-Scl70, anti-histone, anti-U1RNP, anti-Ro/La, antiphospholipid Abs	Small: ANCA, cryo (sent warm), C3/C4, UA Large: imaging, ±optho cs, TA bx (GCA)	Sarcoid: Ca, vit D, limited role for ACE. IgG4: IgG subclasses, C3/C4



DMARD = disease-modifying antirheumatic drug
MTX = methotrexate
SSZ = sulfasalazine
AZA = azathioprine
MMF = mycophenolate mofetil
Biologics = Ab/protein-based Rx (anti-TNF, anti-IL17, anti-IL12/23, CTLA4-Ig, anti-IL1, RTX, TCZ, etc.)
RTX = rituximab (anti-CD20)
TCZ = tocilizumab (anti-IL6)

**Nuances of treatment not encapsulated by this figure – see following pages

RHEUMATOLOGIC ROS

Fevers, arthritis, rashes/photosensitivity, alopecia, nail/nailfold Δ, sicca symptoms, conjunctivitis, uveitis, episcleritis/scleritis, Raynaud's, acrocyanosis, oral/genital ulcers, polychondritis, enthesitis, serositis sx, thromboses, neuropathy, pregnancy loss

LABS

CBC/diff, BMP, LFTs, UA, ESR/CRP, TSH. Target serological testing to positive items on rheum ROS

DDX

Consider malignancy (including paraneoplastic phenomenon) and infection as alternative diagnoses

COMMON INPATIENT RHEUM CONSULT QUESTIONS

1. Inpatient inflammatory arthritis: should this patient have a joint aspiration/injection?
2. Guidance on interpretation/further work-up of positive rheumatologic serologies (i.e., positive ANA (>1:80), +RF, etc.)
3. Work-up/management of fever of unknown origin
4. Patient with history of established rheumatological disease and c/f exacerbation or complication
5. Concern for new onset vasculitis, myositis, or connective tissue disease
6. Work-up/management of new interstitial lung disease (in conjunction with pulmonology)
7. Work-up/management of inflammatory eye disease
8. Guidance on immunosuppressive meds for pt w/ established rheumatologic dz & c/f new infection or malignancy

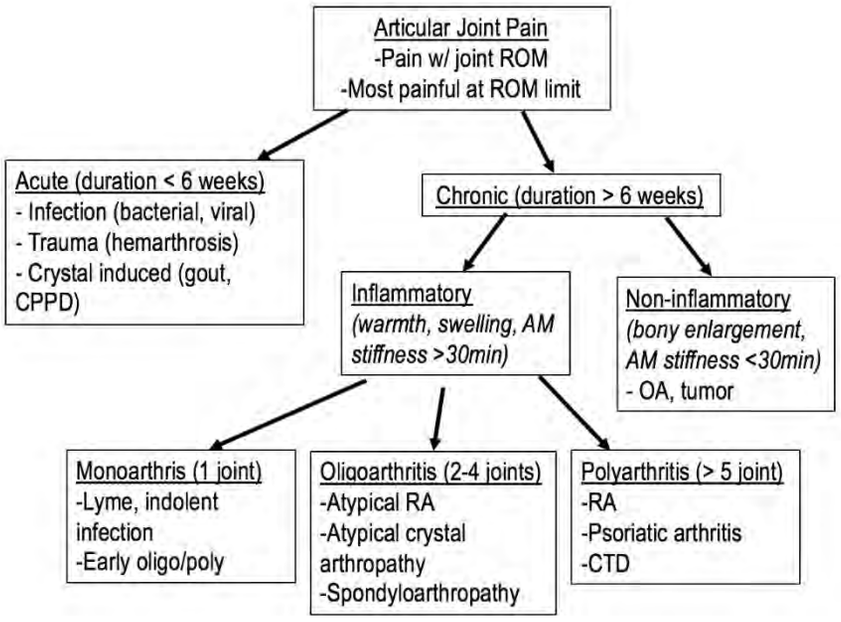
HEALTHCARE MAINTENANCE FOR RHEUM PATIENTS

If prolonged steroids: Ca^{++}/vitD (for bone health), pneumocystis ppx (if ≥20mg prednisone for ≥4 weeks; see ID*: Opportunistic Infections*), PPI (GI ulcer ppx), risk stratification for bone density screening, and A1c (see Endocrine:*Steroid Pearls*). Consider reproductive planning (many meds teratogenic), immunizations, skin exam/sun protection if anti-TNF or MTX (↑skin cancer), increased pap frequency (J Low Genit Tract Dis 2019 Apr;23(2):87-101), and optimizing CV risk w/ primary prev (↑risk w/ chronic inflammation (Lancet Rheumatol 2021;3:e58). Safety labs q3-6 months for most DMARDs (CBCd, CMP).

Rheumatology

Arthritis

Approach to the Patient with Arthritis



Acute Arthritis Syndromes

Arthritis	Joint pattern	Presentation	Diagnosis	Treatment
Gout	- Mono > poly - 1st MTP joint (also called Podagra; 1st sx in 50% pts) -hindfoot, fingers, ankle, knee, wrists	- Triggers: diuretics, meat, seafood, EtOH, HTN, DM2, CKD - Acute flares → chronic arthropathy (tophi) - Urate nephrolithiasis, chronic nephropathy	Gold std: Arthrocentesis: **neg birefringent needle-shaped crystals**, WBC 10k-100k/uL - ACR-EULAR Criteria for Gout can help establish likelihood of dx in absence of joint aspiration - At first dx should obtain plain films to evaluate for erosions/tophi as this changes management - US or dual energy CT if dx remains uncertain	Acute: **colchicine** (1.2mg x1, 0.6mg 1h later, 0.6mg 1-2x daily until 2-3d after resolved) *or* **pred** (40mg QD until resolved then taper) *or* **NSAIDs** (naproxen 500mg BID, indomethacin 50mg TID for ~5-7d), *or* **intra-art steroids** (if 1-2 joints). Choice driven by pt and side effect profile (UTD algorithm to help choose initial therapy). **Anti-IL1 if above contraindicated.** If already on allopurinol, should continue in acute attack. In AKI renally dose. Chronic: **urate lowering tx indicated** if ≥2 attacks/yr, disabling attacks, tophi, or erosions. Check b/l uric acid outside of flare as it can be falsely low during flare. Start ~2 wks after flare or w/ colchicine ppx 3-6 mo to ↓ flare risk **Allopurinol** 1st-line; start low to ↓ hypersens risk, ✓HLA-B*5801 if Korean, Han Chinese, Thai, African descent before starting allopurinol (Clin Pharm Ther. 2013;93:153)
CPPD (pseudo-gout)	- Mono > poly - Knee > wrist, shoulder, ankle - Neck "crowned dens syndrome"	- Can be asymptomatic - Can coexist with gout, OA	- Arthrocentesis: **small pos birefringent rhomboid crystals,** WBC 10k-100k/uL - Chondrocalcinosis	- Acute: if ≤2 joints → **intra-art steroids** (1st line). 2nd line same as gout (**colchicine** w/in 24h sx onset) - Chronic: NSAIDs, colchicine, HCQ, low-dose pred, MTX. Anti-IL1 if refractory - Screen for 2˚ causes: hyperPTH, hypoMg, hemochromatosis, ?low phos
Bacterial septic arthritis	- Mono (50% knee), >1 joint (20%) - Gonococcal: mono or oligo	- Hematogenous spread most common - ↑risk in RA - Gonococcal: fever ± tenosynovitis & skin lesions	- Arthrocentesis: **WBC 50-150k/uL, ↑PMNs,** GS/Cx; blood cx - staph>strep>GNR - Gonococcal: GU NAAT, often ↓ synovial WBC + neg cx - XR ± CT/MRI	- **Antibiotics** for 3-4w (CTX x7-14 d for gonococcal) - Joint drainage/**urgent washout** (ortho c/s) - Often requires hardware explant and longer antibx if prosthetic joint
Viral arthritis	- Varied, but often symmetric poly small joint (e.g. parvo) ± large joint	- Often a/w fever & fatigue	- IgM/IgG/PCR per ddx: parvo, HBV, HCV, HIV, rubella virus or vaccine, chikungunya, dengue, enterovirus, mumps, *Herpesviridae*	- NSAIDs - Antivirals if able - Many etiologies self-limited

CHRONIC ARTHRITIS SYNDROMES				
Arthritis	**Joint pattern**	**Presentation**	**Diagnosis**	**Treatment**
Osteoarthritis	- Poly - Knees, hips, MTP, CMC, PIP, DIP, C-spine, L-spine	- Age >45 - AM stiff <30min, slow progression, no warmth, muscular wasting	- Clinical dx - Bony swelling, joint deformity, limited ROM - XR joint space narrowing, osteophytosis, subchondral sclerosis	- PT, braces, weight loss, Tai Chi - Topical **NSAIDs**, acetaminophen, PRN NSAIDs, duloxetine - **Intra-articular steroids** - If severe, refer to ortho, PM&R - Not recommended: glucosamine, bisphosphonates, PRP (ACR Guideline 2019)
Infectious	- Mono (Lyme: knee, TB: hip), oligo/poly (*T. whipplei*)	- Late Lyme - immunocx or RFs: fungal, TB (indolent monoarthritis) - *T. whipplei:* arthralgias > arthritis, diarrhea, ↓weight	- Arthrocentesis, Lyme serology, T spot, fungal cx, cx/BDG/GM/Ags, SI biopsy (*T. whipplei*)	- Lyme: 4w of doxy or amox - TB, endemic or other fungal: see ID pages - *T. whipplei*: 2w CTX + 1y TMP/sulfa
Rheumatoid Arthritis	- Mono in early stage, then poly - Small peripheral (MCP, PIP, wrists, MTP) - Symmetric	- F>M, age 35-65 - AM stiff >30min - Joint deformity - RA nodules	- Synovitis on exam - **RF, anti-CCP (neg at pres 50%)** - Joint XR for erosions - ESR/CRP can be normal	- Acute: **prednisone** or **NSAIDs**, initiate DMARD if not on already - Chronic: **DMARD** (MTX > HCQ, SSZ, leflunomide); 2nd line combo or **biologic** (infliximab, abatacept, TCZ)
Spondylo-arthritis (SpA): **-Ankylosing spondylitis (AS)** **-Psoriatic arthritis (PsA)** **-IBD-assoc. (IBDa)**	**AS:** mostly axial (spine, SI) **PsA:** can be distal [DIPs], asymm oligo, symm poly, arthritis mutilans, axial **IBDa:** distal oligo or poly arthritis > axial	- AM stiff >30min - Extra-articular: tenosynovitis, enthesitis, dactylitis, uveitis, pyoderma gangrenosum **AS:** Pain in low back, buttock **PsA:** nail pits/onycholysis, 70% with psoriasis **IBDa**: oligo varies with IBD activity, poly or axial has independent course	- Clinical dx - ↑ESR/CRP (not Sn) - HLA-B27 **AS:** ↓spine mobility, bamboo spine + **sacroiliitis** (XR or MRI) **PsA:** CASPAR criteria (91% Sn, 99% Sp), pencil-in-cup DIPs	- **NSAIDs** (1st line) **AS:TNFα inhibitor** (2nd line), anti-IL17, JAKi **PsA:** If mod, **MTX** > SSZ or leflunomide, apremilast (PDEi). - If severe/erosive**, TNFα inhibitor.** If non-response, anti-IL17 or anti-IL12/23. Anti-IL17 can worsen IBD **IBDa:** SSZ > MTX or AZA, **TNFα inhibitor, anti-IL-12/23**
Reactive arthritis	- Oligo > mono > poly (small joints) - Asymmetric - LE > UE	- 1-4w post-infxn*: - Conjunctivitis, urethritis, cervicitis, oral ulcers, circinate balanitis, keratoderma blennorrhagica, SpA sx	- Preceding infection* - Arthrocentesis: GS/Cx - Stool cx (if diarrhea) -Gonorrhea/Chlamydia	- If GU infxn, treat. If GI infxn, may not need to treat - Acute: **NSAIDs** > intra-articular steroids > prednisone - Chronic: if >6mo, **MTX** or SSZ

* Causes: Enteric: *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *C. diff*; GU: *Chlamydia*, *E. coli, Ureaplasma*, *Mycoplasma*

SYNOVIAL FLUID ANALYSIS					
	Normal	**Non-Inflammatory**	**Inflammatory**	**Septic**	**Hemorrhagic**
Clarity	Clear	Clear	Clear-opaque	Opaque	Bloody
Color	Pale yellow	Yellow	Yellow to opalescent	Yellow to green	Red to brown
Viscosity	High	High	Low	Variable	Variable
WBC (per mm^3)	<200	0-2,000	2,000-100K	50-150K	200-2,000
PMNs (%)	<25	<25	≥50	≥75	50-75
Major Ddx		OA, trauma, AVN, mechanical dysfunction	Many: inflammatory and infectious arthritides, rheumatic diseases, gout/CPPD	Septic arthritis; occasionally, noninfectious: gout, reactive arthritis, RA	Trauma, coagulopathy, iatrogenic, tumors, scurvy

Rheumatology — Connective Tissue Diseases

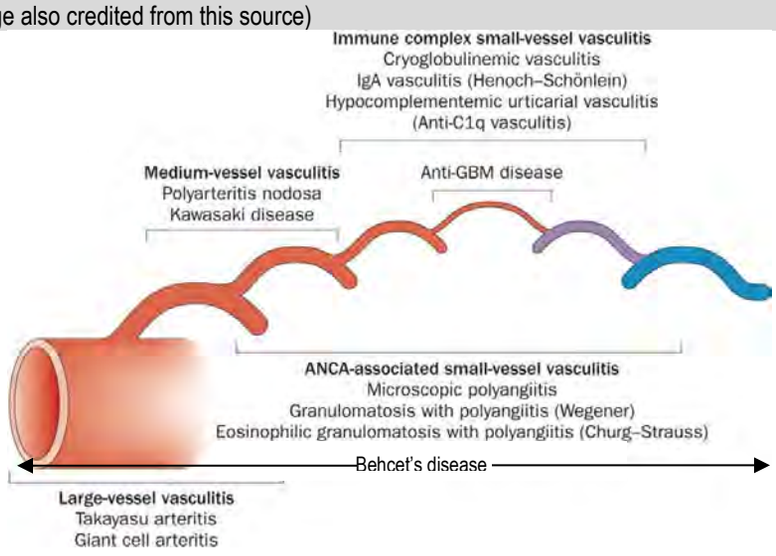
Disease	Clinical Presentation	Work-up	Treatment	Complication
SLE	- F>M, 15-40yo, Afr./Latino-a/Asian descent > White - **Constitutional** sx (fever, wt loss, fatigue, myalgia), **malar** rash (spares NL fold), **discoid** lesions, **photosensitivity**, oral/nasal **ulcers** (often painless), **cytopenias**, serositis, **nephritis**, pneumonitis/DAH/ILD, seizure/CVA/neuropsych, vasculitis - **Arthritis/arthralgia**: migratory, polyarticular (knees, carpal joints, PIPs > other), symmetric, nondeforming. ⊕Morning stiffness.	⊕ANA (>95%; Sn not Sp) ⊕ **anti-dsDNA** (~70%; active dz & lupus nephritis) ⊕ anti-Sm (30%, Sp, remains ⊕ in remission); ⊕ anti-RNP (30-50%); ⊕anti-SS-A/Ro, anti-SS-B/La (35%, 15%) ⊕ antiphospholipid Abs (40%) - CBC/diff, BMP, +DAT, C3/4, ESR/CRP, UA/UPCR; consider RF, CCP if sig. arthritis, (2019 EULAR/ACR Criteria)	*- All (incl. pregn): HCQ (↓flares, clots, death)* - Lifestyle: sun protection, tobacco - **steroids** (goal to taper and d/c if possible). **-** Lupus nephritis: 2024 KDIGO Guidelines **-** If flare/active dz: add immunosuppressive rx (MTX, MMF, CYC, RTX, belimumab, antifrolumab), (Ann Rheum Dis 2024) - Trials of CD19 CAR-T	- CVD (Semin Arthritis Rheum 2013;43:77); ↑ risk **VTE/ATE** (APLS) - Preg. (neonatal death, pre-eclampsia, prem delivery) -ESRD -Osteonecrosis (2/2 SLE and steroids)
Drug-induced lupus (DIL)	- Fever, arthralgias/arthritis, myalgias, rash, serositis. Nephritis uncommon. ~1/3 of isolated cutaneous lupus drug-induced (Br J Dermatol 2012;167:296) - **Months-years** exposure (Ann NY Acad Sci 2007;1108:166) - High risk: **procainamide** (15-20% per y), **hydralazine** (5-10% / y)**.** Mod: quinidine. Low: TNFi, penicillamine, carbamazepine, methyldopa, others	*Serologies/clinical features often **unique** to the **offending drug**. ⊕ **ANA** (almost all cases) ⊕**Anti-histone** (Sn but not Sp for DIL, also in up to 80% idiopathic SLE) ⊖ **anti-dsDNA** (exc. TNFi, IFN) ⊕ **anti-SS-A/Ro** (not Sp) Others: ANCA, anti-RNP	Treat sxs, not antibodies - **Withdraw** offending agent: resolution may take weeks-months - Occasionally NSAIDs, HCQ, steroids for sx - Avoid common DIL drugs in patients with known dx SLE	- Generally good prognosis; life threatening disease is rare and should prompt workup for SLE or other CTD
Sjogren's	- F>M, 40-60y. **Sicca** (dry mouth/ eyes), caries, parotid enlargement, vag. dryness. Extraglandular: fatigue, myalgia, vasculitis, nephropathy, neuropathy, cytopenias, pulm, RA/SLE w/ 2° Sjogren's	⊕ ANA ⊕ **anti-SS-A/Ro** ⊕ **anti-SS-B/La** - Schirmer test, parotid US, salivary gland bx, (2016 EULAR/ACR Criteria)	- Sicca only: sx mgmt.; regular eye, dental care - Extraglandular: immunosuppression rx depends on symptom/organ involved	- 5-10% lifetime risk of NHL, MALT lymphoma - head/neck cancers (Head Neck 2023;45)
Inflammatory myopathies (polymyositis, dermatomyositis (DM), immune mediated necrotizing myopathy, statin induced)	- F:M (2:1), 40-50yo. Symm proximal>distal weakness. dysphagia, constitutional sx, arthralgias, ILD - DM skin findings: heliotrope rash, poikiloderma (chest: V-sign; back: shawl; thigh: Holster), scalp rash, Gottron's papules, mechanic's hands	CK/aldolase, myositis panel Often thigh MRI → muscle bx ⊕ **ANA** (50%), lookup Ab phenotypes: anti-Jo1 (anti-synthetase), anti-Mi2, anti-MDA5, anti-SRP, anti-HMGCR. LDH and AST/ALT (can be normal in amyopathic type DM)	- Induction: **prednisone** - Maintenance: **AZA, MTX** - Resistant/severe: pulse steroids, AZA, MTX, MMF, IVIG, RTX, CYC	- **Malignancy** in DM (25% w/ new cancer dx w/in 3 years of myositis onset, - ILD in 10%
Mixed CTD	- 80% Female - Overlap of SLE, SSc, polymyositis; Raynaud's; non-erosive arthritis	⊕ ANA (often **speckled**) ⊕**anti-U1 RNP** (100%, not Sp)	- SLE fts.: **steroids**, RTX. - If scleroderma sxs, ↓ responsive to steroids	- Main cause of death is **PAH**
Systemic Sclerosis (scleroderma, SSc)	F:M 4:1, 30-50yo. +Raynaud's (almost all), skin thickening, telangiectasias, sclerodactyly, calcinosis cutis esophageal dysmotility, arthralgia Other systemic sx: renal crisis**,** ILD (>70%), PAH (10-40%), digit ischemia Subtypes: **Limited cutaneous** (acral skin involvement, freq. PAH) **Diffuse cutaneous** (diffuse skin thickening, freq ILD). **Systemic sclerosis sine scleroderma –** no skin involvement, + multiorgan involvement	⊕ **ANA** (95%) ⊕ **anti-centromere*** (a/w limited) ⊕ **anti-Scl-70*** (a/w diffuse) ⊕ **anti-RNA pol I,II, or III*** (a/w diffuse, is risk factor for scleroderma renal crisis) - HRCT, PFT, TTE (ILD, pHTN) *Ab are >99% specific (Arthritis Rheum 2013;11:2737)	- **ILD**: MMF, CYC (AZA or TCZ) induc. → MMF, AZA, TCZ maint. If progressive: anti-fibrotic, RTX. (2023 Guidelines) - **PAH**: CCB, riociguat, ERA, PDEi, prostacyclin ag - **MSK**: HCQ, MTX - **Raynaud's**: CCBs - **Skin**: MMF, MTX - **GI**: PPI & promotility	↑cancer risk **Renal crisis** (<20%): ***avoid steroids if at risk (can trigger).*** AKI, abrupt HTN; a/w anti-RNA-pol III; tx w **ACEi** (captopril)
UCTD & Overlap Synd	- Early Raynaud's, incomplete SLE	Dx of exclusion; not meeting criteria for dx of specific ds	Per 1° features	Per 1° features

Rheumatology

Vasculitis

DIAGNOSTIC OVERVIEW (Arthritis Rheum 2013;65:1, image also credited from this source)

- Classified by size and type of blood vessel involved. Large vessels (aorta + branches) vs. medium-sized vessels (named visceral arteries) vs. small vessels (vessels w/o names)



STEP 1 – SUSPECT VASCULITIS

- No "typical" presentation, consider in constitutionally ill pt w/ multisystem organ involvement & evidence of inflammation
- **LARGE** vessel: aorta/branches, e.g. ext. carotid, temporal, ophthalmic → limb claudication, bruits, asymmetric BP, absent pulses, HA, vision loss
- **MEDIUM** vessel: renal/hepatic/mesenteric arteries, etc. → cutaneous nodules, "punched out" ulcers, livedo reticularis, digital gangrene, mononeuritis multiplex (e.g. foot/wrist drop), renovascular HTN, mesenteric ischemia
- **SMALL** vessel: vessels of skin, small airways, glomeruli→petechiae, palpable purpura, glomerulonephritis, alveolar hemorrhage/ hemoptysis, mononeuritis multiplex, scleritis

General work-up:

- **Inflammation**? → CBC/diff (anemia of chronic disease, thrombocytosis, neutrophilia, eosinophilia), ESR, CRP
- **Organ involvement**? → BMP, LFTs, UA + sediment, CXR, brain MRI/MRA (if neurologic symptoms)
- **Suspected large vessel**? →if c/f GCA (HA, jaw claud.,vision Δ), see below. If other sx (GI, limb claud.), consider CTA/MRA C/A/P
- **Suspected medium vessel?** → consider CTA/MRA c/a/p, deep biopsy of cutaneous findings (derm c/s)
- **Suspected small vessel?** → ANCA (will reflex to MPO/PR3 ELISA if ⊕), immune complex w/u (C3/C4, RF, cryo), rash biopsy (derm c/s) (*NB*: ANA/RF not ⊕ in 1° vasculitis; ⊕RF may suggest cryoglobulinemia/endocarditis; ↓C3/C4 in cryo, SLE, 25% of PAN)

STEP 2 – RULE OUT MIMICS and assess for SECONDARY CAUSES: based on presentation (Int J Rheumatol. 2020:8392542)

- **Infections:** (endocarditis, *Neisseria,* chronic osteomyelitis → immune complex deposition; HBV → PAN; HIV, HBV, & HCV → cryoglobulinemia, EBV-associated vasculitis; syphilis & TB → aortitis). **Inflammatory ds:** sarcoidosis, amyloidosis, Susac Syndrome
- **Malignancies/lymphoproliferative:** lymphoma, myeloma, MGUS, IgG4-Related Disease (see *Misc Rheum* page)
- **Coagulopathy/vasculopathy:** APLAS, TTP. If skin necrosis of lower ext., consider cholesterol emboli, calciphylaxis, pyoderma gangrenosum. If renal/internal carotid/vertebral art. involvement/dissections, consider fibromuscular dysplasia.
- **Meds/drugs:** esp. hydralazine, PCN, sulfa, PTU, levamisole in cocaine, immunotherapy, post radiation (see ANCAs in *Autoantibodies* and Drug-Induced Lupus in *Connective Tissue Diseases*)
- **W/u**: BCx, HBV (med-v), HCV/HIV (small-v), syphilis/Tspot (large-v), SPEP/SFLC, tox screen. Consider IgG4, TTE, APLAS panel

STEP 3 – CONFIRM DIAGNOSIS

Tissue biopsy: may be required to secure diagnosis. Sites: skin, sural nerve, and muscle (PAN, ANCA), temporal artery (GCA), kidney (ANCA, IgA), lung (ANCA). Less common: testicle (PAN), rectum/gut, liver, heart, brain (1° CNS vasculitis), sinus (GPA)
Additional imaging: may help support med/large vessel involvement if CTA/MRA non-dx and/or tissue bx infeasible. Generally PET (GCA, Takayasu) or catheter-based angiogram (of celiac/SMA, renal (PAN), chest (Takayasu, GCA), limbs (Buerger's), brain (1° CNS vasculitis))

LARGE-VESSEL VASCULITIS (NEJM 2003 ;349 :160, Arth Rheum 2021 ;1349-1365, Ann Rheum Dis. 2020 ;19-30)

GIANT CELL ARTERITIS: inflammation of aorta & extracranial branches (i.e., spares ICA), often temporal artery (TA). Most common primary systemic vasculitis. Age >50, 3:1 F:M. If <50 yo, rare → consider alternative dx

- **Sx**: constitutional (low grade fevers, fatigue, wt loss, anorexia), new/different HA (incl. scalp tenderness), abrupt visual disturbance (amaurosis fugax, blindness, diplopia), jaw claudication (most specific; fatigue with chewing, NOT PAIN), h/o PMR, ischemic stroke
- **Exam**: asymm BP/pulse; tender/thickened/pulseless TA; bruits; limb/jaw/tongue claud.; formal eye exam; neuro exam
- **Dx**: suspicion should prompt temporal art US & Rheum c/s. ↑ESR (<50 in 10%), ↑CRP. **Gold standard = temporal artery biopsy** w/ granuloma (c/s surg). Unilateral false ⊖ in 30-45% (skip lesions, bx length, laterality, lack of TA involvement, steroids), consider bilateral (↑yield 5%). If c/f large-vessel GCA or bx neg: vessel imaging (PET, CTA/MRA, US w/ similar sens/spec)
- **Rx**: 1st line: High-dose steroids (PO pred 40-60mg qd; if c/f vision Δ, higher dose/IV immediately if ↑suspicion; NEVER delay for Bx. Steroid-sparing: TCZ > MTX=LEF=TNFi > abatacept (Arthritis Care Res 2021;73:1349) ↑ sust. remission w/ TCZ (NEJM 2017;377:317).
- **Polymyalgia rheumatica (PMR)** seen in 50% of GCA pts; 10% pts with PMR develop GCA

TAKAYASU ARTERITIS: "pulseless disease," granulomatous inflamm. of thoracoabd. aorta & branches. Age <40, 8:1 F:M, Asian descent

- **Sx**: constitutional (fever, arthralgias/myalgias, wt loss, night sweats), vessel inflammation (carotidynia, limb claudication), vascular dz (TIA/stroke/sz/dizziness/syncope, MI/angina, HF, mesenteric ischemia). **Exam**: ↑BP, **unequal pulses/BPs** (LE>UE), ↓pulses, **bruits**
- **Dx**: MRA or CTA; arteriography w/ occlusion, stenosis, aneurysms; consider carotid US/Doppler studies, PET-CT
- **Rx**: prednisone 1mg/kg/d; 50% of patients will need 2nd agent for chronic sx (MTX, AZA, TNFi > tocilizumab)

MEDIUM-VESSEL VASCULITIS

POLYARTERITIS NODOSA: systemic necrotizing vasculitis that primarily affects the kidneys, skin, muscles, nerves, GI, joints, but **almost always spares lungs**. Age 40-60, a/w HBV (Arthritis Care Res. 2021;73(8):1061-1070)

- **Sx**: constitutional symptoms (fever, fatigue, weight loss); mononeuritis multiplex (~70% of pts); GI distress (mesenteric ischemia), myalgias; AKI (though GN suggests alternate etiology); gonadal pain (>10%), seizures
- **Exam**: HTN, skin lesions (erythematous nodules, purpura, livedo reticularis, ulcers, bullous eruption, palpable purpura), neuropathy
- **Dx**: gold standard = biopsy (⊖ granulomas; inflammatory infiltrates of vessel wall and fibrinoid necrosis); HBV/HCV, C3/C4, CTA/MRA w/ focal stenosis or microaneurysm (renal/mesenteric)
- **Rx**: prednisone 1mg/kg/d ± MTX or AZA (IV steroids and CYC if severe); antivirals if HBV-related

THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE): segmental inflammatory nonatherosclerotic occlusive intravascular thrombi of small-med arteries and veins of extremities. Age ≤50, 70-90% ♂, strongly a/w tobacco use. (Cochrane Syst Rev. 2016(3): CD011033)

- **Sx:** claudication (arch of foot, calf); Raynaud's (40%), ulcers and digital gangrene; livedo reticularis (hands, feet, & digits); typically ischemic symptoms start in distal vessels and progress more proximally.
- **Dx**: biopsy (rarely) or dx criteria: age, tobacco, distal ischemia (+ABI, thrombophlebitis), ⊕ angiogram/CTA/MRA (segmental dz, abrupt cutoffs, corkscrew collaterals), r/o mimics (PAD, systemic sclerosis, APLAS, thromboembolism)
- **Rx**: **smoking cessation**. Immunotherapy ineffective. Iloprost (PG analog, ↓amputation rates), PCBs for pain, CCB for Raynaud's

ANCA-ASSOCIATED SMALL-VESSEL VASCULITIS (AAV)

PR3-ANCA+ = cytoplasmic staining (proteinase 3 [PR3]; c-ANCA), **MPO-ANCA+**= perinuclear staining (myeloperoxidase [MPO]; p-ANCA)
GRANULOMATOSIS WITH POLYANGIITIS (GPA) (Formerly Wegner's Granulomatosis): necrotizing granulomatous vasculitis commonly affecting the upper respiratory tract (upper and lower airways [90%]), and kidneys (80%), ± cutaneous leukocytoclastic vasculitis (LCV).

- **Sx:** upper respiratory: (sinusitis/crusting rhinitis, subglottic stenosis, saddle nose, otitis media, mastoiditis, hearing loss); lower respiratory: (alveolar hemorrhage, large pulmonary nodules); kidney involvement (crescentic necrotizing glomerulonephritis)
- **Dx**: sinus CT (± bone erosions), Bx w/ **granulomatous inflammation** of vessel walls, PR3-ANCA+ 90%. R/o anti-GBM
- **Rx**: limited disease: MTX + prednisone; severe disease: induction w/ steroids + RTX > CYC (NEJM 2010;363:221; Arthritis Care Res 2021;73(8):1088). Adding avacopan allows ↓ steroids (NEJM 2021;384:599). Maintenance w/ RTX > AZA.

MICROSCOPIC POLYANGIITIS (MPA): necrotizing vasculitis of small vessels without granulomas. All ages (mean 50-60). Similar sx to GPA w/o ENT/upper airway dz; most common cause of pulmonary-renal syndrome (NEJM 2012;367:214)

- **Dx**: MPO-ANCA+ 70%, PR3-ANCA+ rare; BAL; gold standard = skin/renal bx; r/o HIV, cryo, anti-GBM, HBV, HCV**. Rx**: as for GPA

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (**EGPA**) (formerly Churg-Strauss Syndrome): necrotizing granulomatous inflammation of vessels in lungs, skin, nerves, heart (major cause of mortality); ↑**asthma/allergic rhinitis** (asthma precedes vasculitis)

- **Dx**: ≥4 of: asthma, >10% periph. eos, neuropathy, migratory lung infiltrates, paranasal sinus dz, consistent Bx. 50% ⊕ MPO-ANCA
- **Rx**: steroids ± CYC or RTX (if severe disease) or mepolizumab (anti-IL5, if not severe, NEJM 2017;376:1921). Do not delay Rx if c/f mononeuritis (risk of nerve infarction). Screening TTE for all new dx (Arthritis Care Res 2021;73(8):1088)

RELAPSING DISEASE: 5-50% on maintenance therapy; 80-90% w/o maintenance. Dx: often presents as recrudescence of presenting sx; new organ involvement/sx possible but uncommon. Rx: steroids, adjustment of maintenance regimen

IMMUNE COMPLEX-ASSOCIATED SMALL-VESSEL VASCULITIS (Arth Rheum. 2019:1904-1912, N Engl J Med. 2021:1038-1052)

IgA VASCULITIS (HENOCH-SCHÖNLEIN PURPURA): 90% in children; ♂>♀; preceding URI (~10d prior); in adults, ↑severity (↑ nephropathy) and ↑ a/w meds or malignancy

- **Sx**: classic **tetrad** of **1)** palpable purpura (100%, LEs/buttocks = dependent areas), **2)** colicky abdominal pain (50-65%, adults w/ ↓ intussusception), **3)** arthritis (75%), **4)** renal involvement (50%, proteinuria, microscopic hematuria, RPGN) (AFP 2020;102 (4):229)
- **Dx**: clinical dx in children; in adults, confirmation w/ biopsy (leukocytoclastic vasculitis w/ vessel wall IgA dep.) preferred
- **Rx**: children: usually self-limited; adults: may require immunosuppression (orchitis, cerebral vasculitis, pulmonary hemorrhage, severe abd pain/ bleeding) w/ 1-2 mg/kg/day of prednisone or dapsone. (Rheumatology (Oxford). 2019 Sep 1;58(9):1607-1616)

CRYOGLOBULINEMIA: 2/2 immunoglob. that precip. at ↓temp & redissolve w/ rewarming. Most common extrahepatic HCV manifestation.

- **Type 1**: monoclonal (usually IgM or IgG), a/w MGUS, Waldenstrom's, MM. S/Sx:↑ hyperviscosity (↑ in cold) → acrocyanosis, digital ischemia, livedo reticularis, HA, transient CN sx; peripheral neuropathy, GN. Consider sending serum viscosity.
- **Type 2:** "mixed" monoclonal IgM against polyclonal IgG (IgM w/ RF activity), a/w infx (**HCV**/HIV/HBV/EBV, endocarditis), autoimmune dz, malign.
- **Type 3:** "mixed" polyclonal Ig (IgM or IgG) against polyclonal Ig (IgM or IgG), a/w autoimmunity (CTDs, RA, PAN), HCV. S/Sx (type 2 +3): immune complex dep. → **Metzler triad** (palpable purpura, arthralgias, weakness), mononeuritis multiplex, GN.
- **Labs/Dx:** Send C3, C4, RF, HCV, HBV, CBC w/ diff ± infx/rheum labs per sx above**.** Note: blood samples for serum cryoglobulins need to be received warm by lab, wrapped w/ hot pack, w/i 30 min of collection.
- **Rx:** avoid cold in type 1. Tx underlying cause (e.g. HCV, malign.); prednisone ± RTX/CYC; consider plasma exchange in Type 1

VARIABLE-VESSEL VASCULITIS

BEHCET'S DISEASE: vasculitis affecting vessels of all sizes, both venous and arterial; characterized by recurrent oral and genital ulcers and skin/GI/neuro/joint/ocular sx. Age 20-40, more common in Turkey, Middle East, and Asia, a/w HLA-B51

- **Dx:** clinical dx - recurrent painful oral ulcers and ≥2 of: painful genital ulcers (specific), ocular dz (uveitis, retinitis), skin lesions (pustules, folliculitis, papules, erythema nodosum), ⊕ pathergy test (small needle prick elicits red pustule). May have: GI sx (similar to IBD), neurologic sx (migraine, CN abnl, venous sinus thrombosis), vascular dz (ATE/VTE, aneurysms), arthritis (nonerosive/asymmetric). R/o HSV as cause of ulcers.
- **Rx**: (Ann Rheum Dis. 2018;77:808) Mild (arthritis, ulcers): **colchicine**, topical steroid, low dose pred. Apremilast for ulcers (NEJM 2019;381:1918); Severe: **pred** 1mg/kg/d, ±: AZA, TNFi, IFN, CYC, MTX; organ failure (esp ophth.): IV pulse steroids

Rheumatology Miscellaneous Rheumatologic Diseases

Polymyalgia Rheumatica

- Inflammatory condition characterized by proximal muscle aches and AM stiffness. Exclusively in pts >50yrs, peak 70-80yrs, 2:1 F:M.
- **Sx:** abrupt onset symmetrical aching and AM stiffness in shoulders, hip girdle, neck, & torso. Stiffness with inactivity is severe. Can also have fever, malaise, weight loss. Often have limitation of active shoulder abduction.
- **Dx:** Nearly all pts have ↑CRP±ESR. Autoantibodies are negative. EULAR/ACR classification criteria (Ann Rheum Dis2012;71:492).
- **Tx:** prednisone 12.5-20 mg/d w/ slow taper, consider addition of MTX or TCZ if refractory (Ann Rheum Dis. 2022;838-844). Sarilumab (IL-6R) sustained remission in relapsing dz and reduced glucocorticoids (NEJM 2023:389:1263).
- **10% of patients with PMR will be diagnosed w/ GCA at some point.** Screen at initial dx and routinely at f/u visits. See *GCA*

IgG4-related Disease (Ann Rheum Dis. 2015;74:14; Arth Rheum 2020;72:7)

- Fibro-inflammatory condition, involving pancreas, biliary tree, salivary/lacrimal glands, RP, thyroid, & orbits. Mean age ~60. M>F
- **Sx**: **pancreatitis** (w/ otherwise unclear etiol); sclerosing **cholangitis**; sialadenitis; lacrimal gland hypertrophy**; retroperitoneal fibrosis**; orbital pseudotumor; **mass-like** enlargement of pancreas, lungs, kidneys, or any of above organs. Often insidious.
- **Dx**: tissue **biopsy** (storiform ["strawlike"] fibrosis, lymphoplasmacytic infiltrate (↑IgG4+ plasma cells), obliterative phlebitis, tissue eosinophilia); ↑serum IgG4 levels (90% Sn, 60% Sp, NPV 96%, can track with disease activity). May have ↑ serum IgE and ↓ C3/C4
- **Tx**: if sx and/or progressive imaging, **steroids** ± biologics (**RTX**) to induce remission. RTX often for maintenance as well

Sarcoidosis (Int Emerg Med 2018;13:325; Lung 2016:194:91; Am J Resp Crit Care Med 2020;201:e26)

- Systemic inflamm d/o characterized by granulomatous inflammation of virtually any tissue, most commonly **hilar LN**, pulmonary parenchyma, skin, liver, eyes. F>M, young adults. ↑ in Northern pop, ↑ in Black patients
- **Sx**: fever, arthralgias, ↓ wt, fatigue; dyspnea, cough; rash; HSM, LAD; uveitis; cytopenias (BM involvement); pHTN; restrictive CM (sudden death); arrhythmias (AVB; ventricular>atrial); nephrolithiasis; neurosarcoid (CNopathy, periph. neuropathy, meningitis, seizures, hypothalamic dysfn); Lofgren syndr (↑ Sp) = hilar adenopathy, arthritis, erythema nodosum
- **Dx**: definitive dx usually requires **non-caseating granulomas on bx** (skin, LN, EBUS), compatible clinical findings, r/o of mimics. Obtain CXR (CT if atypical). No need to bx isolated asx incidental hilar LAD or if classic syndr w/ ↑ pretest prob of sarcoid (e.g., Lofgren). ↑serum ACE 41% Sn, 90% Sp. Mimics: TB/NTM, fungal, lymphoma, GPA, IgG4, CVID, Berylliosis/Silicosis. Check Cr, alk phos, Ca^{2+} ± 1,25-/25-vitD (granulomas can produce 1,25-vitD), CBC, baseline eye exam & EKG if new dx.
- **Tx**: many do not need tx and can be monitored for resolution/stability. If sx, oral **steroids** ± MTX, TNFi, other DMARDs

Adult Onset Still's Disease (AOSD) (J Rheumatol 1992;19:424; Rheumatol 2023;00:1)

- Rare systemic inflamm d/o w/ fevers, arthritis, rash. Monophasic, intermittent, or chronic. F=M, bimodal (15-25, 36-46 yo)
- **Sx**: fever (often spikes 1-2x daily); arthralgias; evanescent **salmon-colored maculopapular rash** coinciding w/ fever, often truncal, trauma may precipitate (Koebner phenom.); pericarditis; pleuritis; **HLH/macrophage activation syndrome**
- **Dx**: **Yamaguchi criteria** require **≥5 features,** including **≥2 major criteria**
  - Major: fever ≥39ºC for ≥1w; arthralgias/arthritis ≥2w; salmon-colored rash; ↑WBC (≥80% PMN)
  - Minor: sore throat; LAD; HSM; ↑AST/ALT, ↑LDH; negative ANA/RF
  - Other labs (non-criteria): ↑ESR/CRP; **ferritin >3000** (if >10,000, **consider HLH/MAS**, see *Hematology*); ↑plt; ↓Hgb
- **Tx**: Mild: **NSAIDs** 1st line, then glucocorticoids/DMARDs. Severe: **anakinra, pred** 0.5-1mg/kg/d +/- MTX, TNFi, anti-IL6

Relapsing Polychondritis (Rheumatol 2018;57:1532; Clin Exp Rheumatol 2022;40:81)

- Rare immune-mediated d/o a/w inflammation of cartilaginous structures (ears, nose, trachea, joints) & other tissue (eyes), a/w VEXAS
- **Sx:** bilateral auricular chondritis (sparing lobe), nasal chondritis (saddle-nose), arthritis, laryngeal/tracheal chondritis, valvulopathy; eye inflamm; cochlear/vestib dysfunction. **Dx:** ↑ESR/CRP; eval resp/card (CXR/CT ± bronch, PFTs, ECG/TTE)
- **Tx: steroids** first-line; NSAIDs for arthritis; MTX, AZA, biologics for steroid-sparing; CYC if organ-threatening

VEXAS Syndrome (NEJM 2020;383:2628)

- **V**acuolated myeloid/erythroid cells; **E**1 enzyme loss of fnx; **X**-linked (M>F); **A**utoinflammatory; **S**omatic mutations in *UBA1*
- **Sx:** recurrent fever (92%); alveolitis; auricular/nasal chondritis; neutrophilic dermatosis; small to medium vessel vasculitis; cytopenias, macrocytic anemia; thromboses. 60% meet criteria for relapsing polychondritis. Strong a/w myelodysplastic syndrome and MM.
- **Dx:** Genetic testing, consider BMBx. **Tx:** High-dose steroids. Emerging data, often tocilizumab or JAKi. Poor prognosis.

Familial Mediterranean Fever (Am J Med 1967;43:227)

- Autoinflammatory disorder of recurrent fever & serositis. ↑ in Mediterranean descent, onset <10 yo (65%), <20 yo (90%)
- **Sx**: recurrent acute attacks (1-3d, resolve spontaneously) of fever a/w peritonitis (often mistaken for surgical abdomen); unilateral pleuritis; arthritis (monoarticular); skin lesions (erysipelas-like); exertional myalgia; pericarditis; testicular pain; aseptic meningitis.
- **Dx**: During acute attack: ↑ WBC, ↑ ESR/CRP. Check UA for secondary amyloidosis (proteinuria). Genetic testing for confirmation.
  - Diagnostic criteria: requires 1 major or 2 minor criteria (Arthritis Rheum 1997;40:1879)
- **Tx**: **colchicine** (to prevent acute attacks and secondary amyloidosis). 2nd line: anti-IL1 (Ann Rheum Dis. 2016;4:644)

Fibromyalgia (JAMA Intern Med. 2021; 181(1):104-112)

- Central pain processing disorder manifesting as chronic widespread MSK pain, often w/ fatigue, sleep disturbance, and multiple somatic sx. F>M, 20-55 yo. Can coexist with other inflammatory dz like SLE, RA. Often psych. comorbidities.
- **Sx**: widespread MSK pain; fatigue; cognitive disturbance; psych. sx; HA; paresthesia; IBS. "Pan-positive" ROS not uncommon
- **Dx**: clinical: >3 mo of sxs; multiple tender points. Newer criteria (J Pain 2019;6:611). Labs: normal (ESR, CRP, TSH, CBC, BMP)
- **Tx**: Initial: patient education; CBT for pain; graduated **exercise program;** sleep hygiene. Pharmacologic: 1st line amitriptyline, duloxetine, milnacipran; may consider cyclobenzaprine, gabapentin, pregabalin (monotherapy > combo). Avoid opioids

Rheumatology

Autoantibodies

Antibody	Antigen (ANA Pattern if ⊕)	Disease	Comments (See Approach to Rheum Disorders for when to order)
Inflammatory polyarthritis			
RF (IgM)	Fc gamma	RA (50-75%), Sjogren's (60+%), Cryoglobulinemia (90%), others	- Not Sp despite name: RA, CTD, cryoglobulinemia, chronic infxn (e.g. HCV, SBE) - ⊕ in 10% of healthy patients - RA: "seropositive", a/w erosive & extraarticular manifestations (nodules, scleritis, ILD, pleuritis, rare rheumatoid vasculitis)
CCP	Citrullinated peptides	RA (50-75%)	- Most Sp test for RA, ⊕ in 50-75% ("seropositive RA"), a/w erosive dz & extraarticular manifestations. Used for dx only, *NOT* marker of dz activity
Connective tissue diseases (SLE, Sjogren's, SSc, MCTD, UCTD, DM/PM)			
ANA	**When to order**: clinical suspicion for SLE or other ANA-⊕disease (**not** a screening test given high prevalence of false ⊕; **not** to track disease activity). In populations with low prevalence of SLE (e.g. elderly), PPV low given high false ⊕ rates - ANA = antinuclear antibodies (**ENAs** ("extractable nuclear antigens") specify Ag and are a subset of ANAs). Low titer ANA ≤1:160 often false ⊕. If ANA ⊕, order specific autoantibodies guided by clinical presentation; 5% healthy people test ⊕ - ⊕ ANA: MCTD (100%), SLE (98%), scleroderma (90%), drug-induced lupus (DIL, 90%), Sjogren's (60%), PM/DM (50%) - Ddx for ⊕ ANA: *Autoimmune:* autoimmune hepatitis, PBC, IBD, myasthenia gravis, Graves', **Hashimoto's**; *ID:* malaria, SBE, syphilis, HIV, HSV, EBV, HCV, parvo-B19; *systemic inflammation:* lymphoproliferative d/o, IPF, asbestosis*; Medications*		
dsDNA	ds/mtDNA (homogenous)	SLE (40-60%)	- Sp for SLE, a/w SLE ***activity*** (follow titers) & lupus nephritis, consider DIL
Histone	Histones (homogenous)	SLE, drug-induced lupus (90%), Felty's	- Sn but not Sp for DIL - Common meds: **procainamide, hydralazine**, minocycline, phenytoin, lithium, INH, quinidine, terbinafine, TNFi
Smith	snRNP (speckled; ENA)	SLE (30%)	- Sp for SLE, not indicative of dz activity
RNP	U1-snRNP (speckled; ENA)	MCTD (100%), SLE (30%)	- MCTD: high-titer anti-U1 RNP. Also seen in systemic sclerosis (20%)
SS-A/Ro	Ro52, Ro60 (speckled; ENA)	Sjogren's (75%), SLE (40%)	- Can be seen with myositis, PBC, SSc, MCTD. A/w neonatal lupus syndrome, cutaneous lupus. **2% SLE pts have ⊖ ANA but ⊕ anti-Ro**
SS-B/La	La (speckled; ENA)	Sjogren's (40%), SLE (10-15%)	- Sp for Sjogren's, SLE. Usually seen w/ ⊕ anti-Ro. A/w neonatal lupus syndrome
ACA	CENP A-F (centromere)	lcSSc (15-40%)	- A/w limited systemic sclerosis, ↑risk of PAH, ↓risk of ILD, esophageal disease
Scl-70	Topo-I (speckled)	dcSSc (10-40%)	- A/w diffuse systemic sclerosis; ↑risk of ILD, scleroderma renal crisis
RNA pol III	RNA pol. III (nucleolar)	dcSSc (4-25%)	- A/w scleroderma renal crisis, rapidly progressive skin disease, cancer
Fibrillarin	U3-RNP (nucleolar)	dcSSc (<5%)	- A/w PAH, pulmonary fibrosis, & myositis, esp. in African-Americans
PM-Scl	Exosome (nucleolar)	SSc (5-10%)	- A/w limited systemic sclerosis, ↓risk of pulm. & renal dz, ↑risk inflamm. myositis
APL	Phospholipids (on plasma membranes)	SLE (10-44%)	- Lupus anticoagulant (affected by current AC), ELISA for anticardiolipin, anti-B2-glyoprotein. APLAS classification criteria
Myositis			
Jo-1*^	tRNA synthetase (His) (cytoplasmic)	PM/DM (30%), anti-synthetase syndrome (~20%)	- Antisynthetase syndrome: myositis (DM/PM), ILD (70%), polyarthritis, mechanic's hands, Raynaud's, fever
Mi-2*	Mi-2 HDAC factor (homog., speckled)	DM (15-20%)	- More likely in acute DM, good prognosis, a/w disease activity
MDA-5*^	MDA-5 dsRNA binder	DM	- Clinically amyopathic dermatomyositis, rapidly-progressive ILD
TIF1g*	TIF1γ (fine speckled)	Juvenile DM	- A/w malignancy in adult DM
SRP*	Signal recog. particle (cytoplasmic)	PM	- Immune-mediated necrotizing myopathy (degenerating, regenerating, and necrotic cells on bx), rapidly progressive disease course
HMGCR	HMG CoA reductase	myositis	- Immune-mediated necrotizing myopathy, 70% with statin exposure (at any time in past), ≠ statin myopathy (does not respond to discontinuation of statin), very high CPK, often steroid-refractory, good response to IVIG
Vasculitis			
PR3 (c-ANCA)	Proteinase 3	GPA (90%)	- Poor correlation of titer with disease flare/remission - Antibody frequency lower in GPA without renal involvement
MPO (p-ANCA)	Myeloperoxidase	MPA (70%), EGPA (50%), Renal-Limited, DIV (95%)	- Poor correlation of titer with disease flare/remission - Drug-induced vasculitis (DIV): high-titer ⊕ MPO (hydral, PTU, minocycline) (Arthritis Rheum 2022;74:134) - Levamisole vasculitis secondary to cocaine use: MPO or PR3/MPO
Cryo-globulins	Fc gamma	Cryoglobulinemic vasculitis	- HCV > HBV, HIV, CTDs, lymphoproliferative disease, endocarditis - A/w low C4, glomerulonephritis, +RF

* ordered as part of "myositis panel 3"; panel also includes other less common myositis antibodies

^ order separately for faster results if desired

Rheumatology

Rheumatologic Medications

DRUGS	INDICATIONS	COMMON TOXICITIES/NOTES
Ibuprofen, **indomethacin** (short act.) **naproxen** (long acting) **celecoxib** (COX-2 selective inhibitor) **diclofenac** (*Voltaren*, topical)	OA, SpA, RA, gout, CPPD, SSc, SLE	**Gastropathy** (↑ w/ age; ↓ w/ PPI/misoprostol ppx, celecoxib), **kidney injury** (AKI, AIN, papillary necrosis), **CV mortality** (naproxen may ↓ risk, celecoxib noninferior, NEJM 2016;375;2519)
Colchicine; microtubule inhibitor	Gout/CPPD, FMF, Behcet's	**Diarrhea**, **myopathy**, myelosuppression, neutropenia, **med interactions (↓ dose if ↓ GFR)**
NON-BIOLOGIC DMARDS		
Hydroxychloroquine (HCQ, *Plaquenil*)	SLE, RA, Sjogren's, APLAS	N/V, **retinopathy (baseline & q1y retinal exam)**, dizziness, rash, alopecia, myelosuppr., ↑QTc
Methotrexate* (MTX, *Rheumatrex*); DHFR inhibitor (antifolate)	RA (first line), PsA	**Myelosupp. (add folate)**, **↑LFTs**, **pneumonitis** (baseline CXR), GI, stomatitis, rash, teratogen. Monitor: CBC + LFTs q12w
Azathioprine* (AZA, *Imuran*); purine synthesis inhibitor	DM/PM, SLE nephritis, vasculitis (maintenance), RA	GI, ↑LFTs; myelosuppression, lymphoproliferative d/o, bruising. Check **TPMT** deficiency and avoid XOi (allopurinol) as can ↑toxicity (↑ 6-MP)
Mycophenolate* (MMF, *CellCept*); purine synthesis inhibitor	AAV, DM/PM, PsA, Scleroderma, SLE	Cytopenias, ↑LFTS, nausea, diarrhea, HA, insomnia, rash, **teratogen**, lymphoma/skin cancer
Leflunomide* (*Arava*); pyrimidine synthesis inhibitor	PsA, RA	N/V, alopecia, rash, diarrhea, HTN, **hepatotoxicity**, URI, dizziness/HA, **teratogen**
Sulfasalazine* (5-ASA, SSZ, *Azulfidine*)	AS, IBD, JRA, Psoriasis, RA	Sore throat, stomatitis, rash, HA, N/V, myelosuppression; **check G6PD**
Cyclosporine* (CsA); **Voclosporin*** (*Lupkynis*); calcineurin inhibitor (CNI)	SLE nephritis (voclosporin); RA	**HTN, AKI**, HA (both); N/V, GI, gum hyperplasia, hirsutism, edema, tremor (CsA); ↓ HTN & AKI and no level monitoring w/ voclosporin
Cyclophosphamide* (CYC, *Cytoxan*); DNA alkylation	**Severe organ-threatening dz** (SLE nephritis, ANCA)	Myelosuppression, lymphoma, **hemorrhagic cystitis** (MESNA ppx), **infertility** (cumulative dose, leuprolide ppx), teratogen, <1% pneumonitis
Apremilast (*Otezla*); PDE4 inhibitor	PsA/sev Ps, Behcet	N/D, URI, HA, depression, wt loss
Tofacitinib*(*Xeljanz*); JAK1&3 inh. **Upadacitinib*** (*Rinvoq*); JAK1 inh. **Baricitinib*** (Olumiant): JAK1&2 inh.	RA, AS, psoriasis	**Malignancy and CV events** (NEJM 2022; 386:316). Infection, ↑LFTs, diarrhea, **↑VTE**, **death (black box warning**)
BIOLOGICS		
Adalimumab* (*Humira*); anti-TNF **Infliximab*** (*Remicade*); anti-TNF **Golimumab*** (*Simponi*); anti-TNF **Certolizumab** (*Cimzia*); anti-TNF **Etanercept** (*Enbrel*); sol. TNF-R	AS, IBD, Ps/PsA, RA	**CHF (contraindicated in HF)**, HA, nausea, rash, infection, **drug-induced lupus, skin cancer.** Can develop anti-therapeutic Ab -> loss of clinical response. Monitor: CBC, LFTs q3-6 mo *NB*: safe w/ HCV (Expert Opin Biol Ther 2012;12:193)
Rituximab* (RTX, *Rituxan*); anti-CD20 **Obinutuzumab*** (Gazyva); anti-CD20	APLAS, ANCA, IgG4, Scl-ILD, SLE	Infection, HTN, **infusion reaction (use premeds)**, PML, fever, rash/pruritus, LE edema
Belimumab* (*Benlysta*); anti-BAFF	SLE	**Depression**, HA, infusion reaction, PML, GI
Abatacept* (*Orencia*); soluble CTLA4	PsA, RA	Infection, HA, nausea, dizziness, HTN, dyspepsia
Tocilizumab* (*Actemra*); anti-IL6R **Sarilumab*** *(Kevzara*); anti-IL6R	GCA (toci), RA, PMR	Infection, **hepatotoxicity**, HLD, GI perforation (h/o diverticulitis -> contraindicated), neutropenia, thrombocytopenia
Anakinra* (*Kineret*), anti-IL-1R; **Canakinumab*** (Ilaris); anti-IL1β	Gout/CPPD, AOSD/MAS	Myelosupp./neutropenia (anakinra), rash/injection site rxn/pain, HA, arthralgia, fever, N/D (canakinumab)
Secukinumab* (*Cosentyx*); **Ixekizumab*** (*Taltz*); anti-IL17A	AS, Ps/PsA	Infection, IBD flare, diarrhea; neutropenia (ixekizumab)
Ustekinumab* (*Stelara*); anti-IL-12/23 **Guselkumab***(*Tremfya*); anti-IL23 **Risankizumab*** (*Skyrizi*); anti-IL23a	Ps/PsA, IBD	Infection; RPLS, seizures (ustekinumab); HA, diarrhea
Anifrolumab*; anti Type I IFN-R	SLE	Infection, bronchitis/URI, heme malignancies, hypersensitivity
Mepolizumab* (*Nucala*); anti-IL5	EGPA	Injection site rxn, HA
Avacopan* (*Tavneos*); anti-C5aR	ANCA (GPA, MPA)	HA, N/V/D, HTN, rash, ↑LFTs
Intravenous immunoglobulin	APLAS, DM/PM, IMNM, Kawasaki's	Transfusion reactions/anaphylaxis, aseptic meningitis, thromboembolism, HA

*Can ↑ **HBV/TB reactivation** and chronic infection risks **(check HBV/HCV serologies, HIV, and IGRA or PPD prior to starting)**

Endocrinology

Outpatient Type 2 Diabetes Mellitus

SCREENING (Diab Care 2024:47;S26)

- ADA recs: Begin at age ≥35 years, repeat q3y if normal. Repeat q1y if pre-DM. All adults at higher risk = 1) BMI ≥25 (≥23 in Asian-Americans) + RF (1st degree relative with T2DM, nonwhite, history of CVD, HTN, HDL<35, triglycerides >250, PCOS, sedentary lifestyle, acanthosis nigricans) *or* 2) History of gestational DM *or* pancreatitis *or* 3) HIV prior to starting/switching ART. (ADA 2024).

PRE-DIABETES (Diab Care 2024:47;S20)

- Diagnosis: A1c 5.7-6.4%; fasting plasma glucose (FPG) 100-125; or 75g OGTT w/ 2h glucose 140-199
- Monitoring: A1c at least q1y; if A1c 6-6.4%, screen q6mo; at initiation of second-gen antipsychotics & repeat 12-16 weeks after.
- Treatment: **lifestyle Δ** most effective; **metformin** also effective, esp. if BMI ≥35, age <60, or GDM hx (Cochrane Rev 2019)

DIABETES (Diab Care 2024:47;S22) (Diab Care 2023:46;S97)

- Diagnosis: A1c ≥6.5%; FPG ≥126; 75g OGTT with 2h glucose ≥200; or random BG ≥200 & symptoms. Unless diagnosis is made by symptoms & random glucose >200, **confirm with repeat or additional test at the same time or promptly after**.
  - For **T1DM**, check TSH at dx and q1y. Screen for celiac at dx, and again if signs/sx develop. (Diab Care 2024;47;S56)
  - Use plasma blood glucose criteria and not A1C if high RBC turnover: sickle cell disease, 2nd/3rd trimester of pregnancy, ↓G6PD, HD, HIV, recent blood loss/transfusion, EPO tx.
  - A1c less reliable post-partum, with certain HIV drugs, thalassemia and sickle cell (high cell turnover), and anemia (UTD list)
- Tx: goal A1c <7%; can liberalize to <8-8.5% if life expectancy ≤10 years or high risk for hypoglycemia

Healthcare Maintenance for Diabetic Patients (Diab Care 2024:47;S56) (Diab Care 2024:47;S116,S182)	
Every visit	• Review blood sugar log: **goal AM FPG 80-130**, postprandial (1-2h) <180; screen for **hypoglycemia awareness** • Review medication regimen and medication-taking behavior. Screen for tobacco, EtOH, and substance use. Counsel. • Blood pressure: **goal <130/80 (**if it can be safely attained). ACEi/ARB first line. • Weight, BMI: weight center referral if BMI ≥40 or ≥35 with poor control; nutrition referral for all (Obesity Meds) • **Foot exam** (inspect skin, joints, pulses, sensation) esp. if known neuropathy or PVD; ABIs/vascular referral if PVD
Q3-6mo	• A1c **q6mo** if controlled; q3-6mo if A1c above target
Annually	• Lipids: Age 20-39 consider statin if additional risk factors (RF). Age 40-75: moderate-intensity **statin for all DM pts regardless of lipid panel.** If ≥1 ASCVD RF, then high intensity statin w/ target LDL-C<70. Pts with clinical ASCVD (ACS, TIA), target LDL-C<55 with statins + other agents • Urine mAlb/Cr, Cr/eGFR; ACEi/ARB if hypertensive w/ proteinuria *or* GFR <60; refer to renal if GFR <30 • Neuropathy exam: 10g monofilament (+ if no sensation at 4/10 sites, see PCOI); pinprick, vibration, or reflexes • Retinopathy screen w/ dilated eye exam or retinal photography; can consider q2-3y if normal exam(s) • LFTs: consider elastography and/or hepatology referral if elevated to evaluate for MASH • Other: B12 for those on metformin. T1DM – yearly TSH.
Vaccines	• Influenza annually, Hepatitis B series if age <60 and not immune, Zoster, TDAP, Pneumococcus (CDC)

Basal Insulin Management (Diab Care 2024:47;S158)	
Criteria for initiation	• Consider if **A1c ≥9%,** random BG ≥300, fasting BG ≥250, or symptomatic; suspicion for T1DM or LADA; <65yo on two agents with A1c >8% (or ≥65yo and A1c >8.5%) on two occasions >3mo apart; or A1c rising quickly. • Able to perform self-monitoring with glucometer; consider referral to DM educator
Initial dose	• Starting dose: 0.1-0.2U/kg/d or 10U/d (if weight >80kg, may consider starting at 20U/d) • Choice of agent: choose long-acting (glargine qd) ***or*** intermediate-acting (NPH BID → cheaper) • Route: pen (easier to use, more expensive) vs needle/syringe
Titration	• Increase by 2-4U or 10-15% q3d until AM fasting BS is 80-130 without hypoglycemia; savvy patients can self-titrate. • If hypoglycemia occurs or FPG <80 without clear reason, decrease dose by 10-20% or 4U, whichever is greater.

Prandial Insulin Management	
Criteria	• Consider if A1c still not at goal with basal insulin >0.5U/kg/d and fasting glucose within target range (80-130).
Initial dose	• Strategy 1: add 1 rapid-acting insulin before largest meal → start w/ 4U or 0.1U/kg or 10% basal dose • Strategy 2: change to mixed insulin (e.g. fixed 70/30, NPH + regular) BID (before breakfast and dinner). Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM. Confirm w/ pt they eat 3 meals regularly if choosing this.
Titration	• Increase dose by 1-2U or 10-15% q3d until target glucose reached (pre-prandial: 80-130; 1-2h post-prandial <180) • If A1c still not controlled: add rapid-acting insulin to another meal and titrate as above • If hypoglycemia occurs or FPG <80 without clear reason, decrease dose by 10-20% or 4U, whichever is greater

INSULIN SUPPLIES

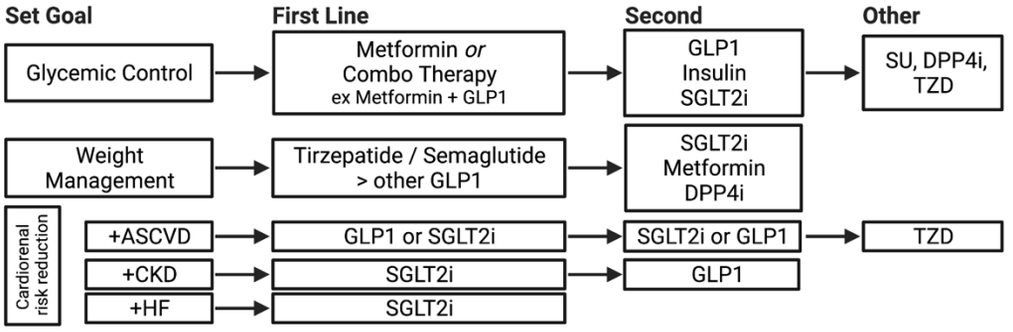
- Needles: Pen needles for pts on insulin pen or 2)needle+ syringe 32G 4mm is less painful (higher gauge = thinner and shorter needle), but larger patients and high insulin doses often require longer/wider needle.
- Syringes: boxes of 100. Choose smallest syringe that will hold the dose (smaller barrel → clearer scale markings)
- Alcohol swabs (or patients can wash hands/skin with soap and water)
- Glucometer & test strips: Many choices, each with own strip brand. Most test strips come in boxes of 50-100. Some glucometers can read BG aloud (helpful for visually impaired). Tip: MassHealth only covers FreeStyle. Otherwise OneTouch Verio usually covered.
- **** All durable medical equipment including test strips and glucometers requires an ICD-10code on the script itself****

Use this barrel size…	With this dose range…
3/10 mL	30U or less
1/2 mL	31-50U
1 mL	51-100U

Endocrinology

Outpatient Type 2 Diabetes Mellitus

Algorithm for Oral Anti-Diabetic Therapy (Diab Care 2021;44:S111) (PCOI)



Non-Insulin Agents (Dual Combination Therapy when A1c ≥1.5% above goal)

Drug/Dose Range	%↓ A1c	Indications/Benefits	Contraindications	Side Effects/Considerations
Metformin: 1st line anti-diabetic medication; many effects, primary mechanism is decreasing hepatic glucose production				
Metformin (Glucophage) 500-1000mg BID	1-2	**First line therapy** Minimal weight loss Improvement in lipids	GFR cutoffs: <45mL/min don't initiate <30mL/min discontinue Metabolic acidosis	**Nausea, bloating, diarrhea** B12 deficiency **Lactic acidosis** in severe liver/renal disease or hypoperfusion state
Metformin pearls: discuss GI sx (decrease over time). Minimize by advising slow titration (250-500mg/wk), taking WITH food, or switching to XR formulation. Benefits/side-effects are dose-dependent – maintain highest dose tolerated.				
SGLT-2 Inhibitors: block renal glucose reabsorption, increase glucosuria				
Canagliflozin (Invokana) 100-300mg qd **Empagliflozin** (Jardiance) 10-25mg qd **Dapagliflozin** (Farxiga) 5-10mg qd	0.8-0.9	**↓CV events, ASCVD mortality, CHF** hospitalization**, CKD** progression (NEJM 2019;380:2295) **Weight loss** ↓risk of hypoglycemia ↓BP 3-5mmHg	GFR cutoffs: Start if eGFR ≥20 mL/min <20 mL/min discontinue History of DKA	UTI & GU **fungal infections** Small risk of **euglycemic DKA** (hold in pts 3-4 days prior to surgery & post-op until take PO) Risk of dehydration/HoTN Risk of fracture (canagliflozin) May ↑LDL cholesterol ? ↑ risk amputation w/ canagliflozin
SGLT2i pearls: Discuss diuretic effect, replace water loss to avoid euglycemic DKA. Initiate 1 mo low dose, then titrate to effective dose. For potency, empagliflozin > canagliflozin > dapagliflozin. HF benefit is probably not a function of A1c lowering.				
GLP-1 Receptor Agonists: stimulate glucose-dependent insulin release from beta cells. Slow gastric emptying, promote satiety and w/l				
Liraglutide (Victoza) 0.6-1.8mg qd **Dulaglutide** (Trulicity) 0.75-4.5mg qwk **Semaglutide** (Ozempic) 0.25-2.4mg qwk	0.5-2 *	**↓CV events, ASCVD** **Weight loss** First line injectable therapy (before basal insulin) ↓risk of hypoglycemia ↑dose↑efficacy (wt/A1C)	**FDA Black Box Warning**: ↑risk medullary thyroid ca. in rodents, not yet demonstrated in humans. Avoid if hx MTC/MEN2 GFR 30-45: avoid exenatide	**GI**: **n/v, diarrhea** **Injection site reactions** Delayed gastric emptying ↑risk of pancreatitis Low starting dose is to avoid GI side fx. Up titrate for effective wt loss/ A1C lowering
Tirzepatide (Mounjaro) GLP1/GIP 2.5-15 mg qwk	2.6			
GLP-1 RA pearls: for weight loss, semaglutide > dulaglutide > liraglutide > others. Up-titrate to effective dose in 1mo intervals.				
DPP-4 Inhibitors: inhibit degradation of endogenous GLP1, ↑glucose-dependent insulin secretion and ↓glucagon secretion.				
Sitagliptin (Januvia) 25mg-100mg qd **Linagliptin** (Tradjenta) 5mg qd	0.5-0.8	Linagliptin preferred if CKD/ESRD ↓risk of hypoglycemia Weight neutral	No contraindications, but very weak	Saxagliptin, alogliptin: **↑hosp for CHF** Joint pain
Insulin Secretagogues: stimulate release of insulin from pancreatic beta cells, thus only effective in pts who still have beta cell function				
Sulfonylureas: **Glipizide** 2.5-20mg qd **Glimepiride** 1-8mg qd	1-2	Affordable	T1DM, DKA Low cross-reactivity in pts with sulfa allergy	**Weight gain** **Hypoglycemia** (esp. glyburide) Possible ↑CV mortality
Meglitinides: **Repaglinide** (Prandin) 0.5-4mg qAC	0.5-0.7	Use like bolus insulin (short-acting) **CKD** ↓nocturnal hypoglycemia	Severe liver disease Concurrent gemfibrozil therapy	**Weight gain** **Hypoglycemia** ↑serum conc. w/ clopidogrel TID dosing
Thiazolidinediones: increase insulin sensitivity by acting on adipose, muscle, and liver to ↑glucose uptake, ↓ectopic lipid deposition				
Pioglitazone (Actos) 15-30mg qd	1-1.6	↓risk of hypoglycemia Possible benefit in NASH	Hx of bladder cancer, renal impairment NYHA Class III/IV HF	**FDA Black Box Warning**: **↑risk of CHF (2/2 ↑ fluid retention)** **Weight gain;** ↑risk of fracture

Endocrinology Inpatient Diabetes Mellitus Management

Insulin Nomenclature

Type (Onset)	Formulation	Peak	Duration
Rapid (10min)	lispro (Humalog) aspart (Novolog) glulisine (Apidra)	30-60 min	~4h
Short (30min)	Regular insulin (Humulin R, Novolin R)	2.5-5h	~6h
Intermediate (1-2h)	Insulin NPH (Humulin N, Novolin N)	4-12h	~12h
Long (3-4h)	glargine (Lantus) qD detemir (Levemir) qD degludec (Tresiba) qD	none	24h

Basal insulin: standing (NOT PRN) fixed intermediate/long-acting for basic metabolic requirements
Prandial insulin: standing (NOT PRN) rapid/short-acting to cover meals
Correctional insulin: sliding scale (can be standing or PRN depending on pt) rapid/short-acting to correct hyperglycemia from prior meal
Pre-Mix (avoid in hospital, but consider for transition to outpatient regimen): combine basal and prandial insulin into one injection
Insulin gtt: use in ICU if BG >180 x2 and anticipated ICU LOS >3 days; reference MICU Insulin Protocol in Partners Handbook. Always overlap with SC insulin by 2-3h before stopping insulin gtt

Inpatient Management (Diabetes Care 2021;44:S211)

- Glycemic targets: Floor: fasting 100-140mg/dL, random <180 mg/dL. ICU: 140-215mg/dL (NOT stricter) (NEJM 2023(13):1180)
- Check BG in: (1) diabetics (2) non-diabetics with gluc >140mg/dL (3) pt w/ therapies a/w hyperglycemia (glucocorticoids, octreotide)
- How to check: **FSBG qAC** (at least for 24-48h) initially OR **FSBG q6h if NPO** or on **continuous** TF or TPN. FSBGs less accurate in hypotension (esp. on pressors), hypothermia, edema, anemia, and Raynaud's/altered blood flow to skin. Confirm with BMP.

Admission Orders (NEJM 2006;355:1903)

1. Hold home oral antihyperglycemic agents when patients are acutely ill (***NEVER hold basal insulin for T1DM***)
2. **Check A1c** in all patients with DM/hyperglycemia if not done in last 3 months
3. If on insulin at home: 25-50% reduction given expected change in diet while hospitalized and initiate ISS for correction and **then adjust basal-bolus dosing over the hospitalization** (Diabetes Conversion Guidelines) (goal 50:50 basal:bolus)
4. If **not** on home insulin:
   a. Well-controlled: start with **lispro** ISS **and change to basal-bolus** once TDD established. Prolonged use of ISS as only anti-hyperglycemic tx is **discouraged (SSI-only reg. suboptimal unless pt well-controlled on orals)** (J Hosp Med 2019;2;114)
   b. Not well-controlled (BG >180mg/dL): start w/ **basal (0.25U/kg/day)**, use 0.15U/kg in pts with ESRD, elderly, and low BMI. Then add prandial insulin (0.05-0.1U/kg) qAC PLUS correctional insulin qAC.
5. **If NPO**: 50% dose reduction or 0.1U/kg/day for basal. Hold prandial & change correctional ISS and FSBG from TID qAC to q6h
6. Correctional insulin sliding scale: use low-dose if insulin-sensitive/ESRD/ESLD/frail, always do TID qAC and MAKE SURE no HS

Adjusting Insulin Dosing: in general, adjust insulin requirement by no more than **20%**. ↓insulin if fasting <100 (hypoglycemia risk).

Fasting/AM BG ↑ (or ↓) from qHS glucose	→	↑ (or ↓) basal insulin dose*
Fasting BG high + qHS BG high but are the same	→	↑ dinner prandial insulin dose (no Δ basal)
BG rises with each meal over the course of the day	→	↑ prandial insulin dose at each meal
Pre-lunch or dinner BG high (w/ other BGs in range)	→	↑ prandial insulin dose of preceding meal

*Avoid titrating basal insulin more than q2-3d (d/t long half life, requires time to reach steady state) to avoid "stacking" and hypoglycemia

1. **Glucocorticoids**: NPH 0.1U/kg/d for every 10mg pred (or equivalent), up to 0.4U/kg/d (dose BID); if dexamethasone or continuous glucocorticoid use, use glargine qD
2. **Tube feeds**: if not on insulin, start with **regular** ISS q6h. Convert to NPH BID based on needs. **If on insulin**, use ½ basal (NPH BID) + ½ bolus (regular insulin q6h) + ISS. **If TF stopped**, give D5W at TF rate until next NPH dose would have been due, and ↓NPH dose by 50% or more based on pre-TF insulin requirements. **TPN**: regular insulin can be added to TPN (discuss w/ nutrition)
3. **Insulin pumps:** consists of basal rate (units/kg/h) which replaces glargine, bolus dose based on carb ratio (units insulin:gram carbs) , and correctional insulin based on the sensitivity factor (units insulin:mg/dL above target glucose). Complications: site infection, pump failure, interrupting infusion. **Endocrine consult required** to develop contingency plan in case of pump failure. **IF CONCERN FOR AMS, TRANSITION TO SUBQ BASAL/BOLUS REGIMEN** (the pump is run ***completely*** by the patient).
4. **Patient's Home CGM:** Can be used to titrate insulin while inpatient but note that often the BG reading is 20-30 minutes delayed and should be cross-checked with FSBG initially. Should not be used in ICU. **Can consult endocrine for help with this.**

Discharge: If oral meds are held inpatient, resume 1-2 days before d/c (ADA, 2023). If poorly controlled DM on insulin PTA: increase home regimen. If new home insulin: nutrition c/s + floor RN teaching and outpatient f/u. Discharge order set: rx for glucometer, test strips, lancets, syringes/vials or pens/needles to MGH outpatient pharmacy and bring up to floor for RN teaching (MGH video link).

Inpatient Hypoglycemia

↑**Risk**: T1DM, brittle DM, malnutrition, emesis, ↓body weight, ↓PO intake, ↓steroid dose, AKI (↓insulin clearance), CKD *(esp. dialysis)*

Beware of hypoglycemia unawareness in T1DM and longstanding T2DM

Manifestations: BG<70: Adrenergic component: shakiness, anxiety, diaphoresis, acute hyperphagia. Neuroglycopenic component: AMS, malaise. <55 with risk of seizure, coma

Treatment: PO (15g gel, tabs, juice) > IV (12.5-25g D50) > IM/SQ (1mg glucagon); recheck in 15min, chase with PO if due to insulin OD

If sulfonylurea OD: 50-75mcg octreotide SQ. **Review and adjust insulin**

Ddx: *If ill/medicated*: drugs (insulin [secretagogues], EtOH), sepsis, ESLD, ESRD, HF, adrenal insufficiency, non-islet cell tumor

If well-appearing: post-gastric bypass (post-prandial, or "reactive", hypoglycemia), insulin or insulin receptor antibodies, insulin (secretagogues), insulinoma (particularly if fasting hypoglycemia)

Insulin	Pro-Insulin	C-Peptide	Ddx
↑	↑	↑	Insulinoma, oral hypoglycemic, autoimmune
↑	↓	↓	Exogenous insulin admin
nl	nl	nl	Non-islet cell tumor, e.g. IGF-2-secreting tumor

Workup: must meet **Whipple's Triad** to merit eval! Triad of 1) sx c/w ↓BG, 2) reliably ↓BG whene sx present,3) sx relief once euglycemic

1. Mixed-meal with postprandial eval (q30min labs for 5h post-meal, or fasting eval with admission for 72h fast)
2. Check: serum glucose, insulin level, C-peptide, βOHB, proinsulin, sulfonylurea/meglitinide screen at time 0

Endocrinology DKA/HHS

DIABETIC KETOACIDOSIS (DKA)

Pathophysiology: think about each element of Diabetic Keto-Acidosis

- *Diabetes*: ↓insulin & ↑opposing hormones (glucagon, catechols, cortisol) → hyperglycemia → osmotic diuresis → hypovolemia
- *Ketones*: ↓insulin → ↑lipolysis → ↑free fatty acids → ↑ketones (acetoacetate, β-hydroxybutyrate, acetone)
- *Acidosis*: ↑β-hydroxybutyrate and acetoacetate, and contraction alkalosis with total body HCO_3 deficit (NEJM 2015;372:546)

Precipitants (the "I's"): infection (30-40% of cases, commonly PNA or UTI), initial presentation of DM (20-25% of cases), insulin non-adherence, inflammation (pancreatitis – but can see ↑amylase/lipase in DKA even w/o this), infarction (MI, CVA, gut), intoxication (EtOH, cocaine), iatrogenesis (e.g., SGLT2 inhibitors, steroids, thiazides, dobutamine/terbutaline, atypical anti-psychotics), infant (pregnancy)

Presentation: dehydration, polyuria/polydipsia, weight loss, n/v/abd pain, AMS, Kussmaul's respirations, fruity breath (acetone)
Dx: BG 250-800, pH <7.3, HCO3 < 18, AG >10, ketonemia. *Consider euglycemic DKA in pt on SGLT2i, EtOH liver dz, pregnancy*

- Check BMP, CBC/diff, UA, SOsm, serum β-hydroxybutyrate, ABG/VBG (if serum bicarb reduced or hypoxemic). Consider hs-trop, EKG, BCx/UCx, CXR, lipase/amylase
  - UA ketone **does not** test for β-hydroxybutyrate, which is the predominant ketone in DKA (must measure from **serum**)
- **Na correction** → *use absolute sodium value* when calculating anion gap. *Use corrected value* to assess for underlying hypotonic hypoNa: Corrected Sodium = Measured sodium + 0.02 * (Serum glucose - 100).

Management: **prioritize ABCs, volume status, identifying precipitant → THEN electrolytes (especially K+) → THEN glucose**
Labs: BMP q2h until AG closes, then q4h until normal K^+; VBG, β-hydroxybutyrate q2-4h; FSBG q1h while on insulin gtt
Step 1: **volume resuscitation** (typically 5-8L deficit) (QJM 2012;105:334; JAMA Netw Open 2020;3:e2024596)

- **Bolus LR** 15-20cc/kg/h for initial resuscitation in first 1-2h (unless CHF, ESLD, ESRD, hypoxemia)
- **Corrected Na** → if **low**, start NS/LR±K^+ at 250-500cc/h; if **normal/high** or hyperCl **acidosis**, start ½NS/LR±K^+ at 250-500cc/h
- **Add D5 to IVF at 150-200cc/h once BG<200 (DKA) or <300 (HHS)**

Step 2: **potassium repletion and management**

Potassium	Action
K <3.3	Give 20-40mEq KCl IV per hour + **hold insulin**!
3.3≤K≤5.3	Add 20mEq K to IVF
K >5.3	Continue to monitor q2h

K+ may be normal/elevated at presentation, but total body K+ is low. Multifactorial causes: solute drag of K+ into extracellular space, osmotic diuresis, ↓insulin not driving K+ into cells. **Aggressive K+ repletion** is critical: *HYPOkalemia will limit your ability to administer the necessary insulin!*

Step 3: **insulin therapy,** see flow chart (Diabetes Metab Syndr Obes. 2014;7:255)
The #1 goal of insulin therapy in DKA is to stop ketogenesis and close the AG

- **Don't start insulin until you have control of K (>3.3meq/L)**
- **Don't stop the insulin gtt** unless true hypoglycemia (<65 mg/dL) or hypokalemia (<3.3 mEq) occurs
- **Initial**: bolus 0.1U/kg regular insulin, then start 0.1U/kg/h IV regular insulin gtt; OR no bolus and start 0.14U/kg/h IV gtt
  - Goal is to ↓BG by 50-75mg/dL each hour
  - For mild DKA, subcutaneous insulin regimens may be used instead of IV (Cochrane Rev 2016)
- **Titrating insulin drip**: **MICU insulin gtt protocol is NOT for DKA**
  - If BG does not ↓ by 10% in 1st hr, re-bolus (DKA) or double the gtt (HHS), no evidence for hourly titration afterwards
  - If BG >250 and falling: increase gtt by 25% if drop is <40, no change if drop is 40-80, decrease by 50% if drop >80
  - Once BG <200 (DKA) or <300 (HHS), ↓gtt to 0.02-0.05U/kg/h and add D5 to fluids
  - Goal BG is 150-200 (DKA) or 250-300 (HHS)

For BG <150	Δ Insulin gtt and glucose source
BG 91-149	↓gtt by 25% + ↑D5 gtt by 50cc/hr
BG 66-90	↓gtt by 50% + ½ amp D50 + continue D5 gtt
BG ≤65	hold insulin + 1 amp D50 + continue D5 gtt

Other electrolytes:

- HCO_3: no proven benefit w/ pH > 6.9. **If pH <6.9**, give 2 amps HCO_3 dissolved in 400mL sterile water w/ 20mEq KCl over 2h
- Phos: total body deficit but serum phos may be ↑/nml; will ↓ w/ insulin; **only replete if <1.0** to prevent cardiac dysfunction

Transitioning to SQ insulin: start if BG **<200** *and* pt is **able to eat** *and* **two** of the following are met: **AG <12, HCO3 ≥15, pH >7.3**

- **Basal** regimen w/ either: home glargine dose *OR* glargine at 0.25-0.4 U/kg/d *OR* glargine at (# units on IV gtt over past 6h x 4 x 0.7). Consider NPH 0.25-0.4U/kg/d in pts presenting with newly diagnosed DM for easier titration (split dose as 2/3 AM dose, 1/3 PM dose).
- **Bolus** regimen w/ either: 0.25-0.4U/kg/d divided (if T1DM or unknown) *OR* ISS only (if T2DM). **Overlap IV gtt/SQ insulin by 2-4h.**

Ketosis-prone diabetes: characterized by DKA w/ hx T2DM or atypical substrate for T1DM (older age, overweight). Patients should be discharged on insulin and see an endocrinologist for antibody (GAD65, IA2) and β-cell function (C-peptide levels) testing to determine diabetes subtype (antibody, β-cell function). Patients may not require long-term insulin therapy.

HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS)

Pathophysiology: hyperglycemia → osmotic diuresis → volume depletion; ketogenesis suppressed by low (but present) insulin levels
Precipitants: same as DKA (note: **pts w/ T2DM and burnt-out pancreas can also present with DKA**)
Presentation: AMS (25-50%), obtundation, seizure, focal neuro def, volume depletion, evolves over **days-weeks** (vs hours-days in DKA)
Dx: glucose >600mg/dL (frequently >1000), osmolality >320mOsm/kg, pH >7.3, absent or minimal ketones
Management: as above for DKA w/ modifications: more aggressive IVF (~8-10L deficit); **goal glucose 250-300mg/dL** (in DKA, 150-200); transition to SQ insulin when BG <300 *and* mental status improved, *and* patient is able to eat. Mortality >> DKA (Diab Care 2014;37:3124)

Endocrinology

Adrenal Insufficiency

ETIOLOGY (Lancet 2014;383:2152; NEJM 2009;360:2328)

Primary AI (Addison's disease): **↓all adrenal hormones → ↑ACTH**. Lesion localizes to bilateral **adrenal glands**

- Causes: autoimmune (80-90% cases in developed countries; anti-21-hydroxylase Ab+ in 86%, autoimmune polyglandular syndromes) >> infection (TB, HIV, CMV, meningococcus, histo > all fungi except *Candida*; most common cause worldwide), bilateral adrenal hemorrhage (infection, DIC, APLAS), infiltration (hemochromatosis, primary amyloidosis), malignancy (mets), genetic

Secondary AI: **↓ACTH → ↓adrenal hormone (glucocorticoids only).** Lesion localizes to **pituitary gland or hypothalamus**

- Causes: Abrupt cessation of chronic supraphysiologic glucocorticoids, meds, pituitary/hypothalamic lesions (see *Pituitary Disorders*)

CLINICAL MANIFESTATIONS (Lancet 2003;361:1881)

Primary AND Secondary:

- Signs/symptoms: weakness, fatigue, anorexia, nausea, vomiting, abdominal pain, psychiatric sx, orthostasis, ↓wt, amenorrhea
- Lab abnormalities: **hyponatremia**, hypoglycemia, hypercalcemia, non-AG acidosis, anemia, eosinophilia, lymphocytosis

Primary only (↓serum aldo): **hyperK (only 65%)**, salt craving, **hyperpigmentation** (↑MSH)**,** n/v, abdominal pain, ↓BP, ↑HR, shock

Secondary only (RAAS intact): ± hypopituitarism, hypoglycemia (more common than in primary AI)

DIAGNOSIS

- **Preferred test:** cosyntropin stimulation test (aka **"cort stim"**) (JCEM 2016;101:364). Can be performed any time of day
  - Check serum cortisol and ACTH → give cosyntropin (ACTH) high-dose 250 µg IV → repeat serum cortisol **30 and 60min later**
  - Normal response: serum cortisol >15µg/dL (note: this rules out all cases of 1° AI + chronic cases of 2° AI)
    - In acute 2° AI, adrenal glands have not had time to atrophy, so cort stim test will be normal
  - If abnormal cort stim, consult endocrine
- **Second line:** If cort stim is not possible, check AM cortisol and ACTH as a preliminary test to suggest AI
  - 6-8 AM cortisol: highly suggestive of AI if ≤3µg/dL (<5µg/dL suggestive); AI ruled out if ≥15 µg/dL (18 µg/dL on older assays).
    - Falsely low: **↓albumin** (cirrhosis, nephrotic syndrome, critical illness; ↓bound and total cortisol, but free cortisol may be nml); PM testing (cortisol level is highest in morning)
    - Falsely high: pregnancy, estrogen tx (↑cortisol binding globulin, ↑bound/total cortisol, free cortisol may normal)
- Testing for **primary** AI: ↑ACTH >2x ULN; ↓aldo, ↑plasma renin, 21-OHase Ab; TB test, VLCFA. Consider CT A/P
- Testing for **secondary, tertiary** AI: ↓ or normal ACTH, normal aldo

ADRENAL CRISIS

- Acute-onset AI with distributive shock in s/o major stressor (infxn, trauma, major surgery, critical illness). ***Consult endocrine.***
- **No known AI**: draw ACTH/cortisol but don't delay empiric treatment; defer cort-stim until stable
- **Known AI or taking chronic steroids**: start treatment; diagnosis can be presumed by history; no role for cort stim test

TREATMENT (JCEM 2016;101:364; NEJM 2019;381:852)

- **Adrenal crisis → stress dose steroids** (**hydrocort 100mg IV x1**) & **>2-3L NS or D5NS** (if hypoglycemic). BMP, cortisol & ACTH. Follow w/ hydrocort 50mg IV q6-8h. Start fludrocortisone 0.1mg QD when off IV fluid (in primary AI & hydrocort dose <50mg in 24h).
  - **Consider in any patient taking glucocorticoids** (>5 mg pred eq/day for ≥4 wk or >40 mg pred eq/day for ≥1 wk)
  - May taper once patient's clinical status improves and *underlying precipitant is adequately addressed*
- **AI** → glucocorticoid: hydrocortisone 15-25mg/day PO (2/3 AM, 1/3 early PM) > prednisone 3-5mg/day (QD or BID) >> dexamethasone (significant Cushingoid side effects) 1º AI: add fludrocortisone 0.05-0.1 mg PO QD (n.b. hydrocortisone has mineralocorticoid activity; dose adjust appropriately); Dose monitoring: hypoK, HTN, edema → reduce dose; New dx: use plasma renin activity (PRA), goal upper normal range; Liberal salt intake, esp. with exercise or exposure to temps >85 ºF (>29 ºC). Consider ↑fludrocortisone dose in summer; Consider DHEA replacement for 3-6 month trial in women with impaired mood 2º AI: assess other pituitary hormone deficiencies (treat AI before hypothyroidism to ↓risk adrenal crisis)
  - **If minor illness (e.g., URI) or minor surgery → sick dose:** "3x3 rule" = 3x daily glucocorticoid dose for 3 days
  - **If severe illness → stress dose:** emergency hydrocortisone injection (as below)
  - Supply patients with medical alert bracelet + card and glucocorticoid injection kit (100 mg hydrocortisone) for emergency use
  - Consider screening for AI diseases (unknown optimal frequency) including DM, thyroid dz, premature ovarian failure, celiac dz

STEROID PEARLS

- Taper: **not necessary if steroid use <3w** (independent of dose) → low risk of HPA suppression. Usually the patient's **specialist** prescribing the steroid a slow taper if underlying disease might flare with an abrupt decrease in steroid dose. Otherwise can drop steroid dose to 5mg pred equivalent and perform a cort stim. If AI present, continue pred 5 mg for 6-8 weeks then repeat cort stim
- Ppx: **PJP**: if taking pred ≥20mg for ≥4w ± 2nd reason for immunocompromise; **PUD**: if taking aspirin/NSAIDs; **osteoporosis**: calcium 1200mg/d + vitamin D 800IU/d if on any dose >3mo (consider bisphosphonates for pts at intermediate/high risk of fracture); **DM2**: monitor glucose/A1C, consider insulin dosing (cover with NPH 0.1 U/kg per 10 mg prednisone equivalents up to 40 mg)

Steroid	Equivalent Anti-inflammatory Dose (mg)	Relative Anti-inflammatory Activity	Relative Na Retention Activity	Duration (hrs)
Hydrocortisone	20	**1**	2	8-12
Predniso(lo)ne	5	4	0.8	12-36
Methylprednisolone	4	5	0.5	12-36
Dexamethasone	0.75	30	0	36-72
Fludrocortisone	n/a	10	125	12-36

HYPOPITUITARISM

Definition: ↓pituitary hormone production/release resulting from diseases of pituitary (1°) or hypothalamus/stalk (2°)
Causes: surgery, radiation, infection (TB, fungal, meningitis), infiltration (sarcoid, hemochromatosis, Langerhans cell histiocytosis, lymphocytosis), TBI, genetic, tumors (1°: pituitary tumors, mets; 2°: external stalk compression [e.g., craniopharyngioma, meningioma, mets])

- 1° only: Sheehan's (infarction), apoplexy (hemorrhage), meds (immune checkpoint inhibitors)

Clinical Manifestations & Diagnosis:

Hormone Deficiency	Signs/Symptoms	Laboratory Tests
Prolactin (rarely isolated)	Reduced lactation	PRL
ACTH (2° adrenal insufficiency)	Weight loss, anorexia, nausea, dizziness	AM cortisol, cort stim test, ACTH
GH	Low energy, central obesity, ↓bone mineral density, ↓exercise performance, psych (depression, immaturity)	IGF-1, insulin tolerance test
TSH (2° hypothyroidism)	Weight gain, bradycardia, hair loss, dry skin, hyporeflexia	TSH, free T4
LH/FSH	amenorrhea/oligomenorrhea, decreased libido, ED, infertility	LH, FSH, estradiol, AM testosterone

Treatment: replace deficient hormone (JCEM 2016;101:3888) and **endocrine consult**. Most sensitive issue is cortisol/thyroid hormone replacement: if concurrent deficiencies **treat AI before hypothyroidism** as can otherwise precipitate adrenal crisis.

HYPERPITUITARISM

Definition: excess of any of the hormones secreted by the anterior pituitary gland (PRL, ACTH, GH, TSH, LH/FSH)
Causes: (1) hyperfxn pituitary adenoma (2) elevated prolactin 2/2 disruption of pituitary stalk, med (e.g. dopamine antagonists)
Clinical Manifestations & Diagnosis: if pituitary adenoma → headaches, visual field deficits (bitemporal hemianopia)

- **Imaging:** MRI brain w/ and w/o contrast (ask rads for pituitary protocol)

Hormone Excess	Signs/Symptoms	Laboratory Tests
Prolactin (Prolactinoma)	Infertility, amenorrhea, galactorrhea (F>M), erectile dysfunction	PRL
ACTH (Cushing's disease)	Weight gain, depression, insomnia, easy bruising, poor wound healing, central obesity, acne, hirsutism, wide violaceous striae, prox muscle weakness, HTN, osteoporosis, DM	Overnight 1 mg dex suppression test, late-night salivary cortisol, or 24h urinary free cortisol excretion
GH (Acromegaly)	Arthralgias, paresthesias (carpal tunnel syndrome), hyperhidrosis, OSA, CHF, enlarged jaw/hands/feet, coarse facial features, deepening of voice, skin tags, hirsutism, HTN	IGF-1, confirm with GH level after glucose tolerance test
TSH (2° hyperthyroidism)	Tremor, palpitation, heat intolerance, weight loss, increased bowel movements, dyspnea	TSH, free T4, total T3

Treatment:

- **Prolactinoma**: if >1cm or symptomatic, first-line treatment is **dopamine agonist** (cabergoline > bromocriptine [preferred in pregnancy]). If <1cm and asymptomatic, can monitor closely with MRI and prolactin levels (JCEM 2011;96:273)
  - Use lowest dose possible to restore prolactin to normal (men and post-menopausal women: <20 ng/mL, pre-menopausal women: <30 ng/mL); TTE **not required** prior to initiation (JCEM 2016;101:4189)
- For all other hypersecreting pituitary adenomas, treatment is **transsphenoidal pituitary surgery** ± radiation therapy
- For GH secreting adenomas in pts who are poor surgical candidates or w/ persistent dz, can tx with somatostatin analog (octreotide)

DIABETES INSIPIDUS (DI)

Definition: polyuria (>50mL/kg/day in DI) in setting of insufficient amount of (central) *or* response to (nephrogenic) ADH
Causes: Central: trauma, surgery, hemorrhage, infarction, neoplasm, infiltrative (sarcoidosis, histiocytosis), infection, autoimmune, drugs (EtOH, phenytoin) || Nephrogenic: drugs (lithium, cisplatin), hypoK/hyperCa, infiltrative (sarcoidosis, amyloidosis, MM), sickle cell
Diagnosis: *confirm polyuria (24 h urine volume >3 L) prior to referral/evaluation*

- **Water deprivation test**: normal physiology: water restriction → ↑SOsm → ↑ADH → ↑UOsm (JCEM 2012;97:3426)
  - Check Na, SOsm, UOsm, UVol q2hr. Urine dipstick for glucose should be negative.
  - If UOsm > 700 mEq/kg, stop test due to appropriate vasopressin response (dx: **primary polydipsia**)
  - Once (1) **SOsm > 295** mEq/kg, (2) **Na ≥145** mEq/L (adequate ADH stimulus) → administer **desmopressin 4 mcg IV**, then check UOsm, UVol q30min x 2hr. judge reponse:
    - UOsm ↑ to <300 mEq/kg → ↑ by <15% **complete nephro DI** || ↑ by 15-45% → **partial nephro DI**
    - UOsm ↑ to >300 mEq/kg → ↑ by >100% **complete central DI** || ↑ by 15-100% → **partial central DI**

Treatment: correct hypernatremia (see *Sodium Disorders*). **Allow patient to drink to thirst. PO preferred to avoid rapid Δ in serum Na**.

- Central: **desmopressin** (exogenous ADH) given intranasal (5mcg qhs + 5mcg qd to tid) or PO/SC, can augment with adjunctive meds. If **impaired thirst** or no access to water, high risk of hypernatremia.
- Nephrogenic: if partial, may try desmopressin; if complete, use adjunctive meds
- Salt/protein restriction: low solute intake reduces thirst, thereby reducing free water intake
- Adjunctive meds: **HCTZ** (volume depletion → increases proximal Na/water reabsorption, decreasing distal Na delivery where ADH acts), **amiloride** (mechanism similar to HCTZ, beneficial in Li-induced nephrogenic DI by blocking entry of Li across ENaC), **NSAIDs** (enhance renal response to ADH), **chlorpropamide** (enhances renal response to ADH)

Endocrinology Calcium Disorders

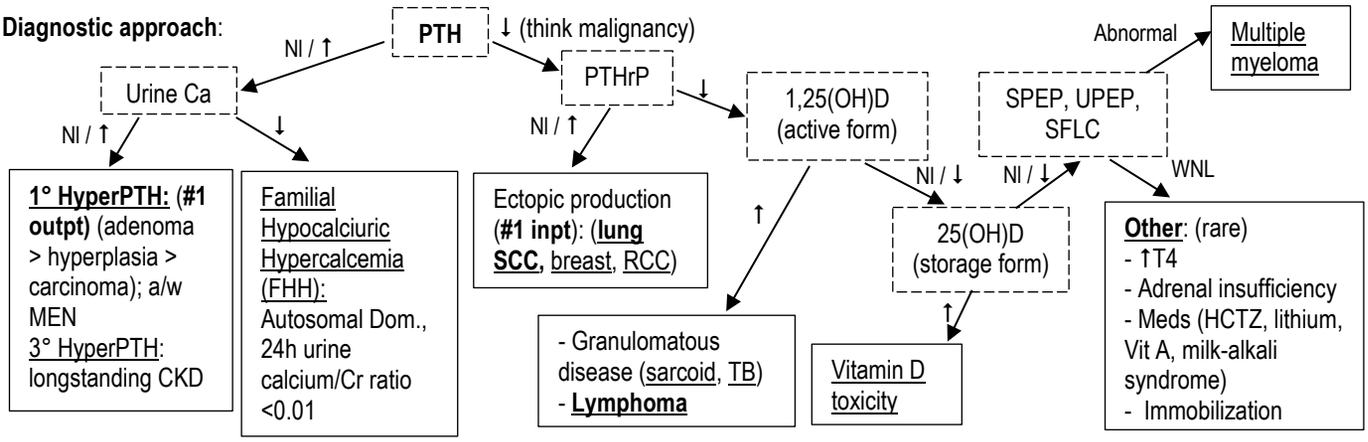
HYPERCALCEMIA

If unsure of validity of total Ca measurement due to hypoalbuminemia or major acid-base disturbances, obtain an iCa. Correction algorithms for albumin are no longer supported (Things We Do for No Reason)

Definition: mild (Ca 10.5-12; iCa 5.6-8); moderate (Ca 12-14; iCa 8-10); severe (Ca >14; iCa >10)

Clinical signs/symptoms: **MSK ("bones")** → osteitis fibrosa cystica (1° hyperPTH), arthralgia, osteoporosis/fractures, weakness; **Renal ("stones")** → polydipsia, polyuria, nephrolithiasis, Type 1 RTA, AKI/CKD; **GI ("groans")** → n/v, anorexia, constipation, ileus, pancreatitis, peptic ulcers; **Neuropsych ("overtones")** → fatigue, depression, anxiety, confusion, stupor, coma; **CV** → bradycardia, short QTc, AV block, valve/vessel calcification, HTN

Diagnostic approach:



Management: (BMJ 2015;305:h2723; NEJM 2005;352:373)

In **mild-moderate** hyperCa: avoid contributory meds; oral hydration; oral PO4 repletion to 2.5-3.0 (IV could lead to hypoCa)

In **symptomatic** or **severe** hyperCa (>14): **should be admitted** for treatment and have an endocrine +/- renal consult to assess HD needs

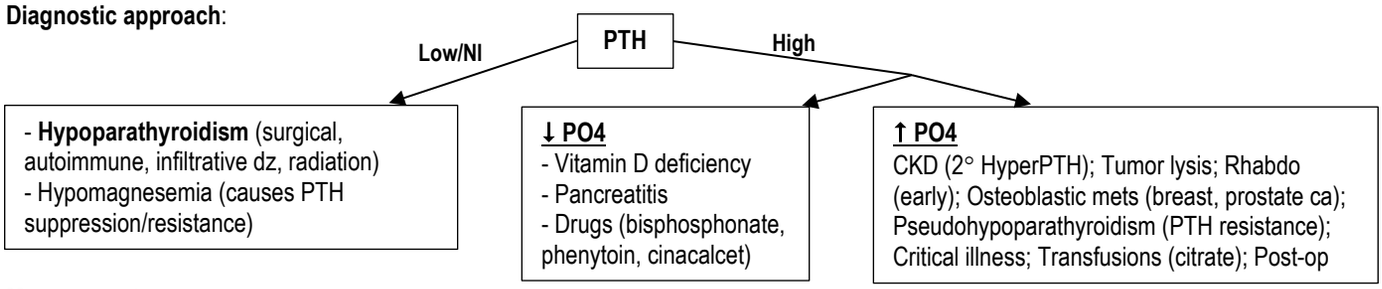
- 1st line treatment: IVF and subQ calcitonin (faster but transient) + IV zoledronic acid (for delayed but sustained effect after 2-4d)
  - Volume resuscitation: pts are typically very dehydrated; bolus NS then gtt @ 200-300cc/h with goal UOP 100-150cc/h.
  - Calcitonin: 4-8U/kg subQ BID x 48 hrs (substantial Ca reduction within 12-24h). Possible tachyphylaxis within 48-72h.
  - Bisphosphonates: zoledronate >> pamidronate (**except in MM**). Takes 2-4d for effect. SE: hypoCa (check vit D, replete prior), hypoPhos, flu-like illness, impaired renal fxn. Reduce rate or dose if CKD (Cr>4.5). Avoid if CrCl <30.
- Other treatments:
  - Denosumab: monoclonal Ab against RANKL → blocks pre-osteoclast maturation. Good option in patients with CKD. May be favored over IV bisphosphonates in hypercalcemia of malignancy, but both can be used if refactory. Requires careful monitoring as hypocalcemia risk >> than with bisphosphonates esp at low GFRs. Check 25(OH)D + replete prior to admin.
  - Loop diuretics: **ONLY** if concurrent HF, CKD (once volume replete), elderly; otherwise avoid 2/2 worsen dehydration
  - Glucocorticoids: for calcitriol mediated etiologies [i.e. granulomatous diseases], takes 2-5 days to take effect.
  - HD: if life-threatening or Ca >18 at onset AND neuro sx.

Special considerations for 1° hyperPTH: surgery is curative. Indicated if (1) symptomatic *OR* (2) asymptomatic with Ca >11.5, osteoporosis/vertebral fracture, CrCl <60, nephrolithiasis, 24-hr urinary Ca > 400mg/day, *or* age <50. If poor surgical candidate, consider **cinacalcet**, bisphosphonate, HCTZ, raloxifene (JAMA Surg 2017;152:878; JCEM 2014;99:3607)

HYPOCALCEMIA

Clinical signs/symptoms: **neuromuscular** (paresthesias, muscle cramps/spasms, tetany, Trousseau sign [carpal spasm w/ BP cuff inflation 94% Sn, 99% Sp], Chvostek sign [circumoral muscle twitch w/ facial nerve tapping poor Sn, 85% Sp]); **seizures**; **↑QTc,** AMS, laryngospasm, bronchospasm, abdominal pain, dysphagia (BMJ 2008;336:1298)

Diagnostic approach:


PTH
Low/Nl
High
- Hypoparathyroidism (surgical, autoimmune, infiltrative dz, radiation)
- Hypomagnesemia (causes PTH suppression/resistance)
↓ PO4
- Vitamin D deficiency
- Pancreatitis
- Drugs (bisphosphonate, phenytoin, cinacalcet)
↑ PO4
CKD (2° HyperPTH); Tumor lysis; Rhabdo (early); Osteoblastic mets (breast, prostate ca); Pseudohypoparathyroidism (PTH resistance); Critical illness; Transfusions (citrate); Post-op

Management:

Replete Mg (hypoCa can be hard to correct w/o first correcting hypoMg (<0.8 mEq/L) → causes PTH resistance and ↓ secretion)

IV Ca repletion: if severe (**Ca <7.5, iCa <1**) or no PO access. Not indicated for asymptomatic hypoCa in CKD.

- 1-2g IV **Ca gluconate** (preferred) or $CaCl_2$ (in codes: via central line, risk of skin necrosis if extravasates) over 10-20 min (slowly to mitigate cardiac risk)-> can repeat in 10-60 min if no effect; **Trend iCa q4-6h** (more reliable given frequent changes in pH in ICU)
- IV therapy ↑serum levels for only 2-3h, chase with gtt or PO; can do sliding scale repletion in ICU

PO Ca repletion: if Ca >7.5 (iCa>3) or asx: 1-2g *elemental* Ca QD in divided doses (Ca citrate better absorbed vs CaCO3 esp. if pt on PPI)

Vitamin D repletion: *See Vitamin D;* often need to give calcitriol for primary hypoparathyroidism.

OSTEOPOROSIS

Definitions: fragility fracture or BMD T-score ≤-2.5 on DXA. **Osteopenia**: T-score -2.4 to -1.1. BMD threshold based on fracture risk in postmenopausal white females, applicable to postmenopausal women and men ≥50 yo (ISCD 2019).

- T-score: SD compared to mean for young, healthy adults of same sex and race
- Z-score: SD compared to mean for age, sex, ethnicity-matched population (preferred younger patients)
- Fragility fracture: occurring spontaneously or from minor trauma (e.g. fall from standing height); fractures of hands, feet, ankles, cervical spine, face, skull typically do not count.

Etiology: (Osteoporos Int 2022;33:2049)

- 1° osteoporosis most common. RFs: age (women ≥65, men ≥70), low body weight (<57.6 kg), FHx of hip fracture, smoking, early menopause, excessive EtOH use
- Many 2°causes, including: kidney and liver dz, hyperthyroidism, hyperPTH, ↓vit D, hypogonadism, hypercalciuria, myeloma, malabsorption, RA, SLE, COPD, drugs (e.g. glucocorticoids, PPI, AED, heparin, aromatase inhib, MTX, GnRH agonists)

Diagnosis:

- FRAX score estimates 10-year fracture risk with or without BMD data. In the US, clinical dx of osteoporosis when FRAX 10-year risk of major osteoporotic fracture ≥20% or hip fracture ≥3%. (Osteoporos Int. 2014;25:1439)
- **Indications for DXA Scan** (spine and hip +/- forearm): all women age ≥65 (USPSTF) and men ≥70; younger if RFs; fracture and age ≥50; hx condition or meds assc. with ↓bone mass or bone loss (Osteoporos Int 2022;33:2049)
- **Initial labs for 2° causes**: CBC, BMP/Ca/Mg/Phos, LFTs, 25(OH)-vitD, PTH, testosterone (men), 24h urinary Ca and Cr
  - Consider TSH, SPEP+sFLC, tTG-IgA, iron/ferritin, homocysteine, prolactin; Urine (UPEP, free cortisol, histamine)

Management: (JCEM 2012;97:1802; JCEM 2019;104:1592; Osteoporos Int 2022;33:2049)

- **Lifestyle measures:** all patients with ↓BMD: weight-bearing exercise 3-4x/wk, smoking cessation, ↓EtOH intake, calcium 1200mg qd (diet+supplement, divided doses ≤500 mg/dose). Replete Vit D to goal 30-50 ng/ml (usually 800-1000 IU/day).
- **Pharmacologic therapy**: initiate in postmenopausal women with hip/vertebral fracture; those with osteoporosis; or those with osteopenia and FRAX 10y risk ≥20% for any fracture, ≥3% for hip; or males >50 yrs with above features & males w/ prostate cancer receiving androgen-deprivation therapy who are high risk of fracture.
  - **Bisphosphonates**: normal Ca, Vit D >20 prior to initiation. Reasses fracture risk and consider drug holiday after 3 years of IV and 5 years of oral bisphosphonates in patients with improved T-score ≥ -2.5 & no new fractures. (JCEM 2019;104:1592)
    - **PO alendronate** 70mg or **PO risedronate** 35mg weekly. Avoid if GFR <30, esophageal dysmotility or h/o bariatric surgery. Strict instructions: sit upright and take on empty stomach w/ full glass of water 30 min prior to other meds/food.
    - **IV zoledronic acid** 5mg annually if esophagitis/GERD with PO treatment, hx bariatric procedures (Roux-en-Y) or otherwise unable to tolerate PO. Can experience flu-like symptoms after infusion.
  - **SERMs (tamoxifen/raloxifene**): less effective compared to bisphosphonates and reserved for use if unable to tolerate bisphosphonate/denosumab or in postmenopausal women with increased risk of breast cancer. Side effects: ↑risk endometrial ca (tamoxifen only), ↑risk DVT/PE, edema, hot flashes, muscle cramps
  - **Referral to Endocrine** for advanced therapies, refractory disease, severe osteoprosis (T score ≤-3.0 or ≤-2.5 with fragility fracture) or age< 50: **denosumab** (RANKL mAb; if discontinued should be started on antiresorptive, preferably a bisphosphonate) (NEJM 2009;361:756; JCEM 2020;106:264), teriparatide and abaloparatide (recombinant PTH and PTHrP analog, respectively) (Lancet 2018;391:230), romosozumab (sclerostin inhibitor)
- **Inpatient** following **fragility fracture**: assess need for surgical treatment and **consult Fracture Liaison Service (p25656).** Bisphosphonates decrease rate of new clinical fracture and mortality post-hip fx (NEJM 2007;357:1799)

Monitoring: variable recommendations; can repeat follow-up DXA hip/spine after 2 years; if stable, can space out scans

VITAMIN D

Definitions: Measured by **25[OH]D (calcidiol)** in serum (JCEM 2019;104:234). No consensus cutoff but most groups use: Vit D Sufficiency: >20ng/mL; Insufficiency: 12-20ng/mL; Deficiency: <12ng/mL; Risk of toxicity >100ng/mL +↑Ca intake

Diagnosis:

- Population screening not recommended, only screen high-risk patients (Choosing Wisely; JCEM 2011;96:1911): Rickets, osteomalacia, osteoporosis, hyperPTH, inadequate PO, ↓ cutaneous synthesis (↓sunlight i.e., institutionalized or northern latitudes, sun pigmentation, aging), malabsorption (gastrectomy, IBD, CF, celiac, pancreatobiliary disease), ↓synthesis (ESLD, CKD), change in catabolism (AEDs, steroids, HAART, immunosuppressants)
- If deficient, obtain PTH, BMP/Phos, ALP, TTG. Consider if insufficient AND concern for secondary cause e.g., IBD

Management (NEJM 2007;357:3; J Am Geriatr Soc 2014;62:147):

- Supplement with D3 or D2 (D3 slightly more preferred but D2 more readily available); recheck levels in 3-4 months
  - <12ng/mL: 50,000IU weekly x6-8w followed by 800-1000IU qd; 12-20ng/mL: 800-1000 IU qd
  - Calcium citrate may be preferred if patient has constipation, is at risk of renal stones or is taking a PPI or H2 blocker.
- For patients ≥65y at high fall/fracture risk: Vit D ≥1000IU + calcium 1000mg qd with goal of serum 25(OH)D >30ng/mL
- For patients with malabsorption: up to 10,000 to 50,000IU qd and/or UVB irradiation
- For patients with ESRD, ESLD, or vitamin D-dependent rickets (poor conversion of 25(OH)D): calcitriol 0.25-1.0 µg qd
- Intermittent, high dosing of Vit D associated with increased falls in older adults and is generally avoided (JAMA 2010;303:18)

Endocrinology Thyroid Disorders & Male Hypogonadism

INPATIENT TFTS

Testing: If thyroidal illness suspected, TSH alone is inadequate; should also test for FT4 & T3. TSH reflects changes within 4-6 wks. *Routine screening on admission not indicated*. Only send if related to CC or suspect thyroid disease (J Hosp Med 2020;15:560)

- **Undetectable TSH (<0.01)** suggests true hyperthyroidism, and **TSH >20 + low T4** suggests true hypothyroidism

Nonthyroidal illness "euthyroid sick": alterations in thyroid fxn due to illness, not 1° endocrine disorder; may be adaptive (anti-catabolic); no indication to treat; most likely cause of abnormal TFTs among inpatients (Lancet Diab Endo 2015;3:816)

- **Typical pattern**: (1) acute illness: ↓↓↓T3, ↓T4, ↓/nl FT4, ↓/nl TSH. (2) recovery phase: ↑TSH → recovery of T4, T3
- Sequential FT4 should ↑ in recovering sick euthyroid but remains low in 1° hypothyroid. rT3 can differentiate central hypothyroidism (↓) from sick euthyroid (↑), but rarely needed. FT3 only helpful to dx hyperthyroidism w/ altered TBG.

HYPOTHYROIDISM

Definition: elevated TSH with low T4 (primary) or inappropriately low/normal TSH with low T4 (2°/central)

Signs/symptoms: general (fatigue, cold intolerance, constipation, dry skin, myalgias, weight gain), neuro (depression, cognitive dysfunction, carpal tunnel), CV (bradycardia [severe], diastolic HTN), irregular menses

- Exam: delayed relaxation phase of DTRs, non-pitting edema, lateral eyebrow thinning, macroglossia

Labs: ↑LDL, ↑triglycerides, macrocytic anemia, ↓Na

- Check other pituitary axes if concern for central hypothyroidism

Workup: TSH with reflex, anti-TPO ab. No role for thyroglobulin or anti-thyroglobulin ab (only useful for monitoring thyroid Ca)

	TSH	FT4
Primary	↑	↓
Central	↓/Normal	↓
Subclinical	↑	Normal

Causes:

- **1°: Hashimoto's** (most common, ⊕**TPO Ab**), infiltrative dz (hemochromatosis, sarcoid), transient thyroiditis (Hashimoto's, granulomatous, postpartum), drugs (lithium, amio, TKIs, contrast), iatrogenic (thyroidectomy, radiation), iodine deficiency
- **2°:** see *Pituitary Disorders*
- ↑ **T4 requirement**: pregnancy, estrogen (↑THBG), weight gain, malabsorptive (e.g., celiac disease), nephrotic syndrome (↑ excretion), rifampin, phenytoin, carbamazepine, phenobarbital

Tx: levothyroxine (T4) starting dose ~1.4mcg/kg/d PO (use 25-50mcg QD for elderly or comorbidities); IV = 50-75% PO

- Take on an empty stomach 1h before food/meds; several hrs apart from calcium, aluminum hydroxide, iron, cholestyramine
- **Check TSH q4-6 weeks and adjust by 12-25mcg** until normal TSH. If pituitary insufficiency/2° hypothyroidism, track FT4s as TSH is not an accurate reflection of thyroid function. **Once on stable dose**, check TSH q6-12 months

Subclinical hypothyroidism: elevated TSH with normal FT4 (biochemical dx)

- Dx: can check anti-TPO Ab (if ⊕, monitor TFTs because at ↑ risk for Hashimoto's)
- Treatment: tx all patients with **TSH ≥10**. If TSH>7 and age<65 OR if age>65 and symptomatic, tx. If TSH 5-6.9, consider risk factors (e.g., CV disease, HLD) to guide tx
- Elderly patients often have higher TSH levels, can be nl, tx if symptomatic.

TSH	Age<65	Age>65
5-6.9	Consider RFs to guide tx	No tx
7-9.9	Tx	Tx only if sx
≥10	Tx	Tx

MYXEDEMA COMA

Definition: Manifestation of severe hypothyroidism, **STAT endo consult**; mortality >30%, commonly 2/2 hypercarbic resp failure

Precipitants: infection, MI, cold exposure, surgery, sedative drugs (esp. opioids) in a poorly controlled hypothyroid patient. Most common in older women with hypothyroidism

Signs/symptoms: **AMS** (**lethargy**/obtundation, +/- coma), **hypothermia**, **hypotension,** bradycardia, ventricular arrhythmias, hypercarbic resp failure, seizure. **Exam**: puffy hands and face, swollen lips, enlarged tongue. **Labs**: ↓Na (be careful with IVF), ↓Glu, ↓T4, ↑TSH

Treatment: **do not wait for lab confirmation to start tx!**

- **Test and empirically treat adrenal insufficiency**: **hydrocortisone** 100mg q8h until AI ruled out. Give steroids **BEFORE T4** (if concomitant AI, replacing thyroid first will catabolize residual cortisol and cause HoTN/death). Draw serum cortisol prior to rx.
- **Levothyroxine (T4)** Loading dose 200-400 mcg IV followed by 50-100 mcg IV QD until able to take T4 orally. Favor low end of range if elderly or at risk of cardiac complications (MI, arrhythmia).
- **Liothyronine** (**T3)** Loading dose 5-20 mcg followed by 2.5-10 mcg q8h, watch for rebound hypermetabolism.
- Monitor FT4 and T3 Q1-2 days, avoiding very high T3 levels.
- Patients are **hypometabolic**: use lower drug doses at lower frequency, avoid mental status-altering meds.

AMIODARONE-INDUCED THYROID DISEASE

Check TSH prior to treatment, q4-6 mo while on amio, and for 1 yr after amio discontinued

- Typical response to amio acutely: ↑TSH (2-3x nl), ↑T4 and FT4, ↓T3, ↑rT3 → levels return to normal in 3-6 months

Amiodarone-induced hypothyroidism: due to Wolff-Chaikoff or thyroiditis

Amiodarone-induced hyperthyroidism

- Type 1: ↑synthesis of T4 and T3 due to ↑iodine, usually will see in pts with latent Graves' or goiter. Seen early during amiodarone Rx **Tx:** methimazole
- Type 2: direct toxicity of drug causing thyroiditis, stored hormone release w/o synthesis. Seen late during or after amiodarone Rx. **Tx:** 40-60 mg/day prednisone x 1-3mo followed by taper
- If unknown: tx with methimazole and prednisone. Rapid response → Type 2, taper methimazole. Poor response → Type 1, taper steroid
- Okay to continue amiodarone, esp. if Type 1 (amiodarone prevents T4 → T3 conversion)

Endocrinology Thyroid Disorders & Male Hypogonadism

HYPERTHYROIDISM (Thyroid 2016; 26:1343)

Definition: low TSH with high T3/T4 (primary) or high/normal TSH with high T3/T4 (secondary/central)
Signs/symptoms: general (↓weight, ↑appetite, heat intolerance, tremor, weakness), CV (palpitations, afib, systolic HTN), hyper-defecation, dyspnea, sweating, anxiety, emotional lability, urinary frequency, abnormal menses, osteoporosis

- Exam: goiter +/- thyroid bruit, lid lag, exophthalmos and pretibial myxedema (Graves' only), hyperreflexia and tremor
- Apathetic thyrotoxicosis: depression, weakness seen in elderly

Labs: ↑HDL, ↓LDL, normocytic anemia, ↑Ca, ↑AlkP, ↑Glu
Workup: 1) TSI and TBII (⊕ in Graves'), 2) RAIU (not for amio-induced or if recent IV contrast), 3) thyroid US w/ Doppler

	TSH	FT4	Total T3
Primary	↓	↑	↑
Central	↑/nl	↑	↑
Subclinical	↓	nl	nl

Causes:

- **1°**: **Graves' disease** (most common, **positive TSI or TBI establishes diagnosis**), toxic adenoma (TA), toxic multinodular goiter (TMG), transient thyroiditis (lymphocytic, granulomatous, postpartum, viral), drugs (amio, iodine, lithium), iatrogenic (radiation, palpation), exogenous T3 or T4 ingestion (low thyroglobulin), HCG-mediated, struma ovarii.
- 2°: see *Pituitary Disorders*

Treatment: β-blocker for adrenergic symptoms (e.g., metoprolol, propranolol)

- Graves' disease: thionamides (methimazole > PTU due to hepatotoxicity, though PTU preferred in 1st trimester of pregnancy), radioiodine (risk of ophthalmopathy), thyroidectomy (watch for hypoparathyroidism). Monitor total T3 and fT4 q6wks.
- If using thionamides: obtain baseline CBC w/ diff (10% of patients have neutropenia that resolves with tx (Clin Endo 2021;94:473)); *risk of agranulocytosis*: routine ANC monitoring not recommended but CBC w/ diff recommended at earliest sign of febrile illness + discontinue drug until result available
- Toxic adenoma or multinodular goiter: radioiodine, surgery, less commonly thionamides

THYROID STORM (Thyroid 2016; 26:1343)

Definition: Manifestation of severe thyrotoxicosis, **STAT endocrine consult**. Mortality rate 10-30%, 2/2 cardiovascular collapse
Precipitants: surgery (any), trauma, infection, iodine load (incl. amiodarone), irregular use/cessation of antithyroid drugs
Signs/symptoms: **AMS** (**agitation**, delirium, psychosis, coma), **hyperpyrexia**, **tachycardia**, atrial arrhythmias, CHF

- Exam: goiter, tremor, warm/moist skin, exophthalmos (Graves')

Labs/dx: ↑T4/T3, ↓TSH, Burch-Wartofsky Point Scale (BWPS) ≥ 45 highly suggestive
Treatment: Patients are hypermetabolic and will clear drugs quickly

- **Beta blocker**: e.g., **propranolol 60-80 mg PO Q4-6H** (only propranolol decreases T4→T3 conversion), doses up to 2g/d. Titrate to sx and HR (i.e., <80). Can also use esmolol gtt for rapid titration (esp. pts who may not tolerate propranolol, e.g., HF)
- **Anti-thyroid meds**: only stop formation of new hormone, not release of stored hormone
  - **Methimazole** (20mg q4h-q6h) is preferred unless pt is critically ill. **PTU** (200mg q4h-q6h) decreases T4→T3 but higher rates of fulminant hepatic necrosis.
- **Iodine** (100-250mg q6h-q8h) blocks release of thyroid hormone, must be given at least 1h after thionamide to prevent use as substrate for new hormone synthesis in TA/TMG; can cause Jod-Basedow (iodine-induced hyperthyroid) in toxic adenoma and Wolff-Chaikoff (iodine-induced hypothyroid) in Graves
- **Hydrocortisone** (100mg q8h) to reduce T4→T3 conversion
- **Cholestyramine** (4 g PO qid) to reduce enterohepatic recycling of thyroid hormone
- **Plasmapheresis** for those unable to take thionamides and urgently being prepared for thyroidectomy

MALE HYPOGONADISM (J Clin Endocrinol Metab 2018;103:1715)

Definitions: Clinical syndrome that results from a failure of the testes to produce physiologic levels of testosterone and/or normal number of spermatozoa due to pathology at the testicular level (1°), hypothalamus/pituitary (2°), or both

- 1° causes (Low T, High FSH/LH): Klinefelter, cryptorchidism, testicular radiation, orchitis, myotonic dystrophy, HIV
- 2° causes (Low T, Low FSH/LH): hyperprolactinemia, obesity, Fe overload, opioids, glucocorticoids, androgens (e.g. supplementation), progestins, GnRH agonists
- 3° causes (rare): impaired GnRH signaling due to tumors, radiation to the brain, Kallmann, severe malnutrition.

Signs/Symptoms: loss of axillary/pubic body hair, reduced libido, erectile dysfunction, gynecomastia, low sperm count, decreased energy, depressive mood, normocytic anemia, reduced muscle bulk, increased body fat, osteoporosis
Diagnosis:

- Measure 8am-10am fasting total testosterone x2 (nl total T range ~ 300-800)
  - Measure free testosterone only if c/f Δ in SHBG (obesity, nephrotic syndrome, steroids, HIV, cirrhosis, thyroid dz)
- If testosterone level is low on both measurements, measure LH/FSH to determine 1° vs 2° etiology
  - If 2° measure Fe studies, other pituitary hormones, & consider imaging (see *Pituitary Disorders*); for 1° consider karyotype.

Management:

- **Testosterone therapy** is the mainstay of treatment to induce/maintain 2° sex characteristics and address symptoms
  - Formulations: intramuscular (weekly, q2w, and monthly), transdermal gel, patches, tablets
  - SE: site reactions, acne, oiliness of skin, no large RCT to study cardiovascular risk/MACE or VTE
  - Contraindications: prostate ca, breast ca, erythrocytosis, severe BPH, untreated OSA, severe LUTS, planning fertility

Monitoring:

- Evaluate around 3-6mo after initiation to assess response to treatment and measure concentrations, then annually
  - Goal level is mid-normal physiologic range (300-800)
- Check baseline Hct and 3-6mo after tx, if Hct >54% stop therapy, re-initiate at reduced dose once Hct reaches safe level
- If patient chooses to monitor for prostate ca, perform DRE and measure PSA before treatment and 3-12mo after starting (NEJM 2023)

ADVERSE DRUG REACTIONS (ADRS) (Allergy 2019; 74: 1457)

KEY History: Drug, date, dose, route, doses/days into course, co-administered meds, coinciding infections, sx, severity (home/office/ED/hospital/ICU), treatment given, exposures since
Document appropriately in EPIC allergy section. Include rxn, date, intolerance vs reaction, other meds tolerated

ADRs defined by WHO as any noxious/unintended/undesired drug effect that occurs at doses used for prevention, diagnosis, or treatment.

- **Type A =** predictable (85-90%): dose-dependent reactions related to a drug's known pharmacological action which occur in otherwise healthy patients if given sufficient dose and exposure (e.g., gastritis after NSAIDs)
- **Type B =** unpredictable (10-15%): dose-independent, unrelated to pharm action, occurs only in susceptible pts
  - **Drug intolerance**: undesirable effect that occurs at low and sometimes subtherapeutic doses w/o abnormalities of metabolism/excretion/bioavailability (e.g., tinnitus after aspirin)
  - **Drug idiosyncrasy**: abnormal effect caused by underlying abnormalities of metabolism/excretion/bioavailability (e.g., hemolysis after antioxidant drug in G6PD deficiency)
  - **Pseudo-allergic reaction** (formerly known as anaphylactoid): direct release of mediators from mast cells and basophils rather than IgE antibodies (e.g., flushing during vancomycin infusion, exacerbation of asthma/rhinitis w/ aspirin in AERD, opiate pruritis)
  - **Drug allergy** (5-10% of all ADRs): immunologically-mediated hypersensitivity reactions, including IgE mediated

HYPERSENSITIVITY REACTIONS (Gell and Coombs Classification) (Clin All 1998;18:515)

Type	Reaction	Mechanism	Presentations	Timing
I	IgE-mediated, Immediate	Ig-E mediated degranulation of mast cells due to antigen binding and cross-linking of IgE Anaphylaxis Pathway	Anaphylaxis, allergic rhinitis, allergic asthma, urticaria, angioedema, hypotension	Min-hrs (usually 1 hour)
II	Antibody	IgM/IgG antigen interactions on target cell surfaces	Drug-induced cytopenia	Varies
III	Immune-complex	Immune complex formation & deposition in tissues → complement activation → local/systemic inflammation	Serum sickness, vasculitis, drug induced lupus	1-3 wks
IV	Cell-mediated, delayed	Ag activates T cells → Ag later binds to activated T cells → cytokine release → macrophage & cytotoxic T cell accumulation	Contact dermatitis, SJS/TEN, DRESS, AGEP	Days to weeks

CLINICAL MANIFESTATIONS OF DRUG ALLERGY (AACI 2018;14:60)

Organ	Manifestation	Clinical Features	Timing	Causative Drugs
Skin	Urticaria, angioedema, drug exanthem, SJS/TEN, AGEP	For information on skin manifestations of drug allergy, see *Dermatology: Drug Eruptions*		
Blood	Hemolytic anemia, thrombocytopenia, leukopenia		Varies, but in general: -Hemolytic anemia: acute -Drug-induced TMA: acute or subacute	PCN, sulfa drugs, AEDs, cephalosporins, quinine, heparin, thiazides
Liver	Hepatitis, cholestatic jaundice		Varies, can be acute or chronic	Sulfonamides, phenothiazines, anti-TB drugs, carbamazepine, erythromycin, allopurinol
Kidney	Interstitial nephritis, glomerulonephritis		Varies, days to months	PCNs, sulfonamides, allopurinol, PPIs, ACEi, NSAIDs
Multi-organ	Anaphylaxis	Urticaria, angioedema, bronchospasm, GI, hypotension	Immediate (usually within 1 hr)	Abx, NM blockers, anesthetics, contrast, recombinant proteins (e.g., omalizumab)
	DRESS	Rash, fever, eos, hepatic dysfunction, LAD	2-8 weeks	AEDs, sulfa drugs, minocycline, allopurinol, mAB (monoclonal Ab)
	Drug induced lupus erythematosus	Arthralgias, myalgias, fever, malaise	Months to years	Hydralazine, procainamide, INH, quinidine, minocycline, abx, anti-TNF
	Serum sickness	Arthralgias, urticaria, fever	1-2 weeks	Heterologous Ab, infliximab, mAbs, allopurinol, thiazides, abx, bupropion
	Vasculitis	Cutaneous or visceral vasculitis		Sulfa abx and diuretics, mAbs, hydralazine, levamisole, PTU

DIAGNOSIS (Drug Allergy Practice Parameter 2010)

- **Labs** (sometimes helpful): CBC w/ diff (eos), LFTs, Cr, tryptase (if anaphylaxis), auto-Abs (e.g., anti-histone in drug induced lupus)
- **Skin testing**: evaluates for drug-specific IgE antibodies for a limited # of meds. NPV of penicillin skin testing = 95%.
- **Deliberate rechallenge = graded challenge = test dose procedure**
  - Used when there is a **low suspicion for true allergic reaction** to a medication. Does NOT assess cross-reactivity of structurally-related drugs. Contraindication = severe non-IgE mediated HSR (ex: DRESS, SJS, etc.)
  - **How to order**: **Antibiotic Test Dose** in Epic order sets (can also type "penicillin" "allergy" "test dose")
    - Automatically orders the rescue medications, nursing communication orders, and fills in doses of desired med (FYI test dose = 1/10 of rx dose for IV meds and ¼ of rx dose for oral meds)
  - If **no reaction**: patient is *not* allergic to that agent and can safely receive it, **please update allergy list**
    - If agent was a related agent (e.g., CTX administered in PCN-allergic pt): update "comments"
    - If agent was same agent as recorded allergy (e.g., PCN administered in PCN-allergic pt): remove allergy
  - If ⊕ **reaction**: Anaphylaxis pathway: Epi 1:1000 IM (0.3 mg), Benadryl 50mg IV/PO, page allergy fellow, & complete a Medication Safety Report.

DRUG DESENSITIZATION (JACI 2010;125:S126) | Ellucid-Drug Desensitization and Test Dose Administration

- **Indications**: ⊕skin test, ⊕test dose, or h/o severe type I HSR **AND** no alt. tx. ONLY for Type I (IgE-mediated) rxns
- **Method**: administer drug with increasing doses over hours such that it induces state of **TEMPORARY** tolerance
- At MGH, consult Allergy. Generally, desensitization needs to be done in the ICU but there are exceptions (e.g., chemo, aspirin)
- **If patient discontinues medication**: procedure must be performed again if pt stops medication for >2-3 half-lives

PENICILLIN & CEPHALOSPORIN ALLERGY | Ellucid -Penicillin and Cephalosporin Hypersensitivity Pathway

- 10% of pts report a PCN allergy, but **90%** of patients with a h/o PCN allergy can tolerate PCN (JACI 2010;125:S126)
- 80% of pts with IgE-mediated allergy to penicillin will lose their penicillin sensitivity over 10-year period (AAAI 2019; 321:188)
- Patients with PCN allergy have a **<1% cross reactivity to carbapenems** (CID 2014;59:1113); and **<2% of patients w/ skin test-proven sensitivity to PCN will react to cephalosporins** (Annals 2004;141:16)
- Allergic determinants of cephalosporins can be derived from the **beta-lactam structure**, but in later (3rd/4th gen) cephalosporins, they are most commonly derived from the R-group.
- Refer for outpt PCN skin testing if (Allergy Referal) if: unclear reaction and likely requirement for that drug in the future
- See Penicillin Cephalosporin Hypersensitivity Pathway for guidance on inpatient test dose procedure in pts reporting PCN allergy

OTHER COMMON DRUG ALLERGIES

- **Taxanes/platinum-based Chemotherapy**: differentiate *infusion reaction* (SIRS response) from anaphylaxis (type I HSR). Platinum agents assoc with IgE HSR. Taxanes generally non-IgE mediated, premed usually effective (AAAAI 2009;102:179)
- **Allopurinol hypersensitivity syndrome**: rash, fever, hepatitis, AKI usually within 4-8 wks. Testing for *HLA-B5801* in pts at elev risk (patients of Southeast Asian descent and African American) recommended prior to starting (ACR Guideline 2020)
- **Aspirin/NSAIDs** (JACI 2021; 148:283): wide spectrum of drug-induced allergic reactions, including exacerbation of underlying respiratory disease, urticaria, angioedema, anaphylaxis, and rarely pneumonitis and meningitis
  - Management: avoid NSAIDs (COX-1 inhibitors). If NSAIDs are necessary (ie aspirin for ACS), consult Allergy.
  - **Aspirin-Exacerbated Respiratory Disease (AERD)** (aka Samter's Triad): triad of asthma, rhinosinusitis w/ nasal polyps, and ASA/NSAID sensitivity (nasal congestion, bronchospasm). **Tx**: Avoidance of NSAIDs, desensitization and daily uninterrupted therapy, leukotriene-modifying drugs, or biologics (omalizumab, mepolizumab, dupilumab) (JACI 2021; 148:283)

IV CONTRAST MEDIA (ACR Guidelines 2021) | Ellucid -Allergy Premedication | *See Contrast* for details on contrast reactions

Type/Path	Epidemiology	Presentation	Clinical pearls	Pre-Treatment (MGH protocol)
Pseudoallergic Direct stimulation of mast cells / basophils	Mild rxn: 0.6% pts Severe rxn: 0.04% pts	Immediate pruritus, urticaria, angioedema, airway obstruction, HoTN, abd pain. Called pseudoallergic bc not immune rxn -can still cause danger.	**Seafood allergy is NOT** a contraindication. **Oral contrast is NOT** contraindicated in a patient with IV contrast allergy, very rare pseudo-allergic reactions.	***Elective*** (13h protocol) Prednisone 50mg PO at 13, 7, & 1h prior AND Benadryl 50mg PO 1h prior ***Urgent*** (4-5h) Methylprednisolone 40mg IV now & q4h until scan AND Benadryl 50mg IV 1h prior ***Emergent (no data)*** (1h) Methylpred 40mg IV AND Benadryl 50mg IV @ 1h prior
Delayed T cell-mediated	0.5-14% of patients	>1h - 1 wk. Usually mild, skin eruption. Can be more severe	**Tx**: Supportive care	Unknown efficacy to steroid/antihistamine ppx. Not specifically advocated

Danielle Crabtree

Allergy & Immunology — Angioedema & Anaphylaxis

ANGIOEDEMA (Allergy 2018;73:1393) | (Int J EM 2017)

- **Definition**: localized non-pitting swelling of skin or mucosal tissue due to interstitial edema; Usually affects areas of loose connective tissue including face, throat, lips, extremities, genitals, bowels. Often asymmetric. Occurs in min-hrs after exposure and resolves within 1-3d. **Common triggers**: food, insect bites, drugs, temp, delayed pressure, solar, vibratory, cholinergic, contact, and aquagenic

Type	Symptoms	Triggers
Histamine (mast-cell mediated)	Localized swelling **Urticaria/pruritis** Bronchospasm +/- hypotension	Common allergens, ASA, NSAIDs, CCB, opioids, contrast dye, tPA, platinum-based chemo, β-lactams, metoprolol, sirolimus/everolimus, risperidone, idiopathic/spontaneous
Bradykinin	Localized swelling w/in 24-36h exposure Abd cramping/pain **NO urticaria** Usually longer w/ worse symptoms	**ACEi**: 0.1-0.7% pts; may occur any time during treatment and recur 4-6 wks after cessation. Consider also in ARBs, DPP-4 inhibitors. **C1 inhibitor deficiency:** Either due to AD inheritance (present at early age) or acquired (usually lymphoproliferative disorder). Screen: ↓C4, normal C3. **Hereditary Angioedema:** begins in childhood, worsens in puberty. Prodromal sxs include erythema marginatum **TPA mediated angioedema**: tPA activates complement system and leads to ↑ histamine release and ↑ bradykinin levels.

- **Work up:** CBC w diff, BMP, LFTs, CRP, ESR, C4 level, C1 inhibitor level, C1 inhibitor function, & tryptase (see below)
- **Treatment**: in ALL patients **ABCs, secure airway**; involve ENT for awake **nasotracheal** intubation
  - **If urticaria, multisystem involvement, or underlying illness/infection**: remove exposure → treat like anaphylaxis (see below)
  - **If no urticaria/pruritis**: **1 gram TXA** (bradykinin-mediated angioedema does not respond to epinephrine or steroids)**:**
    - On ACEi**:** stop ACEi → supportive care (if severe, consider treating similar to Hereditary Angioedema [mixed evidence]), add ACEi to allergy list
    - Known hereditary or acquired angioedema**:** page Allergy for C1-inhibitor (ecallantide, **icatibant)**. **FFP** 2nd line.
    - Not on ACE; no known disorder**:** H1 antihistamines + methylpred → PO pred (5-7 d taper) + H1 antihistamine
- **Follow-up**: Place Allergy/Immunology referral on discharge

ANAPHYLAXIS (JACI 2020,145:4) | (AAAI 132:124-176) | Anaphylaxis Treatment Protocol

Type	Mechanism	Triggers
Immunologic	IgE mediated	Food (e.g., nuts, shellfish, milk, eggs), insect venom, meds (e.g., NSAIDs, β-lactams, biologics), latex, occupational allergens, aeroallergens
	Non-IgE mediated	NSAIDs, HMW dextrans, biologics, contrast
Nonimmunologic	Direct mast cell activation	Physical factors (exercise, heat, cold, UV light, XRT), EtOH, meds (opioids)
Idiopathic	No apparent trigger	Mastocytosis/clonal mast cell disorder, previously unrecognized allergen

- **S/Sx**: (1) Cutaneous = angioedema, urticaria, flushing, pruritis; (2) Respiratory = dyspnea, wheeze, upper airway angioedema, rhinitis; (3) GI = nausea, vomiting, diarrhea; (4) Cardiovascular = hypotension**. Can have biphasic reaction**: resolution w/ return of symptoms 1-72h (usually <12) after initial symptom resolution despite no further exposure to trigger (4-20% pts)
- **Diagnostic criteria**: **1 of 3** must be met
  1) Acute onset (min-hr) of **skin ± mucosal** involvement AND either **respiratory sx** *OR* **hypotension (age appropriate)**
  2) Two or more of the following after exposure to **LIKELY allergen**: skin/mucosa swelling, respiratory sx, HoTN, persistent GI sx
  3) **Low BP** (SBP<90 or >30% drop from baseline) after exposure to **KNOWN allergen** for patient
- **Labs**: **tryptase** (within 15min-3h of symptom onset & 24h after sx resolve to establish baseline). Values ≥1.2x baseline + 2ng/dL = mast cell activation. Normal levels do not rule out anaphylaxis (normal in 37%). Consider plasma histamine (peaks in 5-15 min).
- **Treatment**: **Establish and maintain airway**, administer oxygen/IVF (1-2L) and lie pt flat/Tberg for hypotension, remove trigger
  - **Epinephrine**: **1st line**. ONLY medication that reverses airflow obstruction & prevents cardiovascular collapse. Dosing: **epinephrine (conc 1mg/mL) 0.3-0.5mg IM** in mid-outer thigh. May repeat **q5-15min**; if >3 doses required, consider continuous epi gtt (1-10mcg/min). If on beta blockers AND resistant to epinephrine, glucagon (1-5mg bolus → gtt @ 5-15mcg/min)
  - Adjunctive agents: **Albuterol** (stacked nebs x 3) PRN wheezing/cough/SOB
    - **H1 antihistamines**: PRN for pruritis/urticaria. *Does NOT treat airway obstruction or hypotension!* Benadryl 25-50mg
    - **H2 antihistamines**: famotidine 20mg IV or PO
    - **Methylprednisolone IV or IM:** 40mg if weight <120kg, 80mg if weight >= 120 kg. No evidence to prevent biphasic rxn. May be beneficial if (1) severe sx requiring hospitalization (2) known asthma (3) significant and persistent bronchospasm
  - **Make sure to discharge home with EpiPen & refer to Allergy**
  - If h/o anaphylaxis to stinging insect, refer for skin testing. If +, consider SQ venom immunotherapy, which decreases risk of subsequent anaphylaxis from 50-60% to 2-3% (NNT = 2) (NEJM 2014;370:1432)

Natalia Sutherland

Allergy & Immunology — Mast Cell Disorders

MAST CELL BASICS (NEJM 2015;373;163)

- When activated, mast cells degranulate and release **vasoactive & pro-inflammatory** mediators such as histamine, heparin, serotonin, leukotrienes, prostaglandins, proteases (including tryptase), cytokines (including TNF), etc.
- Signs and symptoms associated with mast cell activation are similar to those of allergic & anaphylactic reaction. However, **angioedema, hives and wheezing are uncommon in mastocytosis.**
  - Cutaneous: flushing, pruritis, urticaria, angioedema
  - GI: heartburn & nausea (histamine → hypersecretion of acid from parietal cells), diarrhea, abdominal cramps
  - Cardiovascular: tachycardia, hypotension, presyncope, and syncope
  - Neuro: fatigue, lethargy, memory and concentration problems, headache
  - Respiratory: wheezing (bronchospastic cough), nasal congestion
- **Triggers for mast cell activation**: temp changes (e.g., hot showers), exercise, alcohol/spicy food ingestion, mechanical irritation, stress, insect stings, certain medications (opioids, NSAIDs, muscle relaxants). *Can also be spontaneous.*

MASTOCYTOSIS (JCCN2018;16:1500)

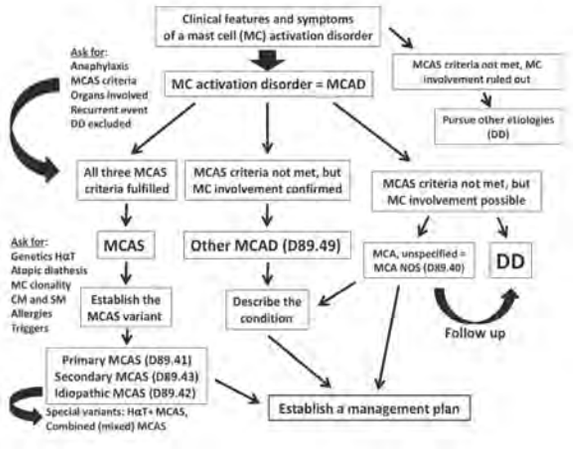
- Heterogenous group of **rare** disorders (~1:10,000) characterized by excess mast cell proliferation and accumulation.
- Symptoms are primarily related to episodic release of mast cell mediators (lasts 30 min – few hours)

Mastocytosis	
Epidemiology	Primarily presents as systemic mastocytosis (SM) Rare presentations of cutaneous mastocytosis (primarily in infants and young children)
Organ systems	Multifocal **infiltration of mast cells** in various internal organs **Bone marrow** is involved in virtually **all patients** **Skin** more common with indolent systemic mastocytosis.
Variants	1. Indolent SM (most common): no end-organ dysfunction 2. Smoldering SM 3. SM associated with non-mast cell hematologic neoplasm 4. Aggressive systemic mastocytosis: + end-organ dysfunction 5. Malignancy: mast cell leukemia, mast cell sarcoma 6. Cutaneous only: urticaria pigmentosa (UP), mastocytoma of skin, diffuse cutaneous mastocytosis
Cutaneous manifestations	Due to mediator release = flushing, pruritis, urticaria Due to mast cell infiltration = maculopapular cutaneous mastocytosis (most common; fixed, salmon/tan lesions; predominate on trunk/limbs), bullous eruptions, mastocytomas, telangiectasis
Systemic manifestations	• GI (50%): n/v/bloating, chronic diarrhea, chronic abdominal pain, steatorrhea, GERD, gastroduodenal ulcers, hepatomegaly. Liver infiltration: ↑alk phos, AST, ALT, GGT, portal HTN, ascites if advanced SM. • MSK: fibromyalgia-like pain, osteoporosis (due to prolonged TNF/IL-6), sclerotic/lytic lesions • CV: episodes of tachycardia, hypotension, vasodilation • Heme (50%): anemia (most common), thrombocytopenia, eosinophilia, LAD, splenomegaly • Neuro: anxiety, mood disorder, insomnia, depression, headache, hypersomnolence, irritability • Systemic: fatigue, cachexia
Characteristic clinical presentations	• Recurrent symptoms of mast cell degranulation • Urticaria pigmentosa (UP) +/- Darier's sign* • Hypotensive anaphylaxis, especially with stinging insects • Unexplained osteoporosis and pathologic bone fractures • Sclerotic or lytic bone lesions prompting malignancy eval • Suspected hematologic disease (heme abnormalities, splenomegaly, fatigue, weight loss) ***Darier's Sign:** If UP detected, rub affected skin. Erythema/urticaria around lesion within 5 mins suggestive of mast cells within lesion.
Lab findings	Elevated baseline serum tryptase **(>20ng/mL)** in **non-symptomatic state** strongly suggestive of SM.
Diagnosis	BMBx/aspirate. Mast cell collections in affected organ. A/w KIT gain of function mutation. See WHO dx criteria).

MAST CELL ACTIVATION SYNDROME (MCAS) (JACI 2022;10:1941-50)

Recurrent episodes of symptoms of anaphylaxis (hives, swelling, HoTN, diarrhea, SOB) w/o consistent trigger and w/o clonal population of mast cells.

- Dx criteria: 1) **episodic, objective s/s of mast cell release involving ≥2 organ systems** AND 2) **corresponding elevations in mast cell mediators** (preferred: tryptase 120% bl + 2ng/mL) AND 3) **respond to medications that stabilize MC/inhibit MC mediators/block mediator release** (e.g., anti-histamines, cromolyn, anti-leukotrienes). Less-preferred for #2: urine histamine/PGD2 metabolites >200% individual's baseline, less specific
- Tx: anaphylaxis tx as indicated, otherwise H1/H2 blockers, ASA, anti-leukotrienes, omalizumab (blocks IgE). BWH Mastocytosis center
- For those w/o clear dx, provisional dx "Other MCAD" while search for other causes of sx (see diagram, JACI 2022;10:1941-50)
- DDx "other MCAD": other urticaria, *angioedema*, food intolerance/aversion & GI d/o, rheum/joint d/o, acute/chronic infx, endocrine/neuro d/o, intoxication/poisoning/med effects, psych d/o.

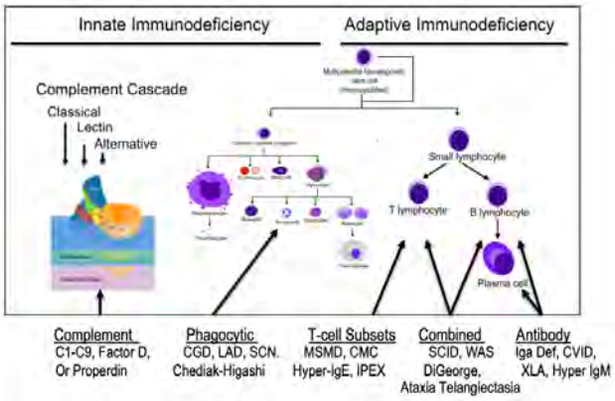


Allergy & Immunology — Primary Immunodeficiency

Primary Immunodeficiency Disorders (JACI 2016 1109-1110,)

Definition: inherited deficits of immune system → increased incidence/severity/frequency of infections

- Prevalence: 1/1200-2000 pts
- Warning signs in adults: ≥4 infection requiring antibiotics/year (ear infxn, sinusitis, bronchitis, PNA, otitis media), infection not responsive to antibiotics, ≥2 severe infections (osteo, septic arthritis, meningitis, sepsis), ≥2 PNA within 3 years, chronic diarrhea, recurrent deep abscesses, persistent fungal infection, persistent thrush, infection w/ benign mycobacteria, relevant FH
- H&P: developmental hx, FH, age at onset, frequency & type of infections, syndromic features, autoimmune dz,
  - Most severe forms are on MA newborn screen; mild forms go undetected into adulthood (e.g. antibody def)



- Need to r/o 2° causes of immunodeficiency (HIV, immunosuppressants (rituximab and other mAbs, chronic glucocorticoid use), malignancy, radiation, cirrhosis, diabetes, nephrotic syndrome, SLE, RA, asplenia)
- General principles of management: vaccination, abx ppx, ↑risk of malignancy, immunoglobulin replacement, HSCT

	Disorder	Presentation	Infectious Organisms	Testing (JACI 2018 38: 129-143)
INNATE	**Complement** (5%)	Any age - Sinusitis, PNA, meningitis (recurrent nisserial infections) → think late complement def (C5-C8) - Lupus-like syndrome → early complement def C1/C1s/C2/C4a/b - Rheumatoid disorders - Atypical AUS - Protein losing enteropathy	Bacteria: encapsulated esp. Neisseria, gonococcal infections	Complement levels: C1q, C1s, C2, C4, Factor H, Factor I, Thrombomodulin, CD46, C1 inhibitor, CD59, CD55 CH50+AH50 (alt pathway)
	Phagocyte abnormalities (10%)	Infancy/childhood - Oral, lymphadenitis, skin and soft tissue, liver, lung, bone, anorectal - Unusually severe infections - Granulomas, poor wound healing	Bacteria: S aureus, PsA, Serratia, Klebsiella, non-TB mycobacteria, nocardia Fungi: Candida, Aspergillus	ANC (↓SCN, ↑LAD), ELANE gene in SCN, Oxidative burst via DHR/NBT test for CGD, Other tests to order for: SCN gene abnormalities, WAS, CSF3R, MKL1, G6PD, GATA2, CYBB, NCF1, *On outpt Invitae genetic panel
ADAPTIVE	**T cell subset defects** (5%)	Infancy - Oral thrush - Diarrhea (enteropathy) - Respiratory Infections - ILD - pancytopenia	Bacteria: Mycobacteria Viruses: CMV, adenovirus Fungi: Candida, PJP	Flow cytometry Anergy/proliferation tests STAT1, AIRE if chronic mucocutaneous candidiasis or APECED, FOXP3 (IPEX), IL2RA, CTLA4
	B cell / Antibody (65%)	>6 mos, can present in adulthood - Recurrent sinusitis, otitis media, PNA, bronchiectasis - Chronic GI malabsorption, diarrhea - Autoimmune disease (29% in CVID) (Blood 2012;119:1650) - Anaphylaxis to blood products (IgA deficiency)	Bacteria: H flu, Strep, Staph, Moraxella cat, PsA, mycoplasma pneumoniae Virus: Enterovirus (esp. with IgA deficiency) Parasites: Giardia	SPEP (IgG, IgA, IgM), IgG subclasses, flow cytometry **Vaccine response** Polysaccharide PPSV23 titers: ≥70% of serotypes ≥1.3 = adequate. If not, give PPSV23 & repeat titers in 4-6 wks Protein: tetanus, diphtheria IgG Conjugated: Hib IgG
	Combined B & T cell (15%)	<6 mos old, FTT - Oral thrush, viral infections - Chronic diarrhea - Absent thymus - Active disease to live vaccines - Autoimmune cytopenias	Bacteria: Salmonella, Listeria, non-TB mycobacteria Viruses: CMV, EBV, VZV Fungi: Candida, Aspergillus, cryptococcus, histoplasmosis Parasites: PJP, toxo, Cryptosporidium	B Cell Enumeration (CMF) As above for B & T cell deficiencies Adenosine deaminase deficiency Avoid live vaccines

Immunoglobulin Replacement (JACI 2017;139:S1)

- Manufactured using donor pools of donated human plasma & contains IgG antibodies, administered as IVIG or SQ Ig
- **Replaces antibodies** and is **anti-inflammatory** by inducing autophagy in cells associated w/ Th1 inflammation.
- Starting doses: 400-800 mg/kg q3-4 wks for trough level >500-600 mg/dL (higher in pregnancy & bronchiectasis)
- Consider HBV serologies prior to IVIG: can't check for 3-4mo after IVIG. If patient already got IVIG, consider HBV PCR
- **IVIG in infection** depends on host & infection. If CVID w/ infection, can check IgG levels. Beneficial in CMV pneumonitis in solid organ tx recipients, rotaviral enterocolitis & bacterial infections in lymphoproliferative dz (e.g., CLL)

Therapeutic Use of Vaccines in Patients with PID (JACI 2018;141:474)

- **ALL** patients with PID can receive **INACTIVATED** vaccines according to routine schedule. Prioritize flu, HPV, PNA. For **LIVE ATTENUATED** vaccine safety/benefit, see UpToDate Table
- Pts on **IVIG** have adequate titers to measles, mumps, varicella, rubella, pneumococci, Hib, and meningococcus (variable). If exposed to an infection requiring "hyperimmune" Ig (rabies, HBV, tetanus), should still receive pathogen-specific Ig.

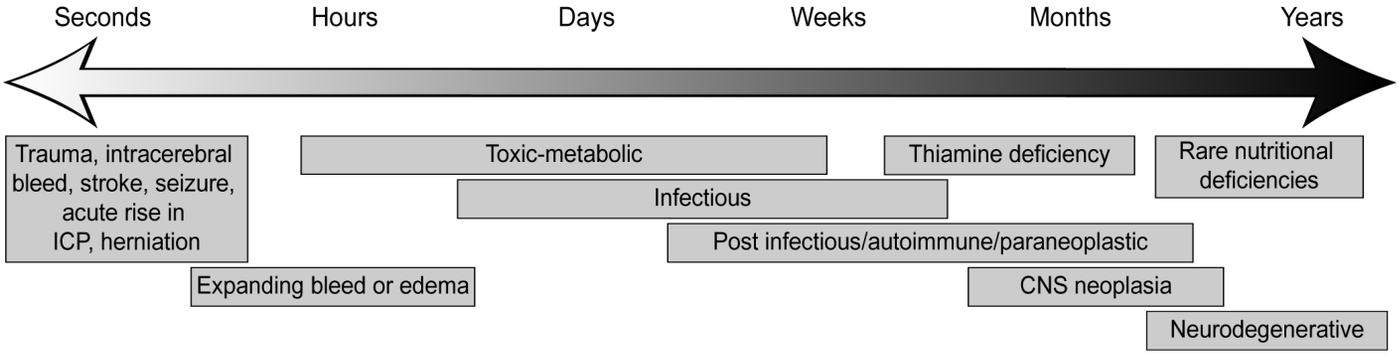
Neurology

Altered Mental Status

CAUSES OF AMS

- AMS is any change in patient's baseline mental status and can include obtundation/non-responsiveness, agitation, lethargy, disorientation, hypoactivity, hyperactivity, etc.
- Major categories include 1) Metabolic, 2) Infectious, 3) Drugs/Toxins/Medications, 4) Primary CNS, 5) Delirium
- Duration: **flow diagram (below)**

AEIOU TIPS: **A**lcohol (intox, HE, withdrawal/DTs, Wernicke's)/**A**rrythmia, **E**lectrolyte (high or low Na/iCa/Mg/Phos)/**E**ndocrine (glucose, pituitary, thyroid, parathyroid, adrenal), **I**nfection (sepsis vs 1° CNS: encephalitis, meningitis, abscess), **O**xygen (hypoxia, hypercarbia)/**O**verdose (opiate), **U**remia/**U**rine retention, **T**rauma/**T**umor/**T**TP/**T**emp, **I**atrogenic (see MAR below), **P**sych/**P**oison, **S**eizure (+post-ictal)/**S**troke/**S**yncope



APPROACH TO ACUTE AMS

- **ABCs & vitals**: call **Rapid Response** (+/- **RICU** if concern for airway, +/- **Code Stroke** if focal or high risk for head bleed/clot)
- **Hx**: baseline functional status, last known well, time course, previous AMS, recent clinical events, past medical history (i.e. neurodengerative disease/dementia, hx CVA, seizure disorder, cranial mets)
  - **MAR**: (stopped/started, withdrawal/overdose) insulin, benzo, opioid, steroid, anticholinergic, antihistamine, antiHTN, AED, anti/dopaminergic, digoxin, Li, ASA, OTCs, MSK relaxers, abx (**cefepime/**cephalosporins, PCNs, FQs) (Neurology 2016;86:963)
  - Consider catatonia, NMS, serotonin syndrome and see *Catatonia, NMS, & Serotonin Syndrome*
- **Neuro Exam**:
  - Arousable (GCS): commands, attention, cranial nerve or focal weakness, abnormal movements/nystagmus/ataxia, meningismus
  - Not arousable: coma exam: pupils, nystagmus, doll's eyes, corneal, grimace, cough/gag, w/d to pain, posturing (JNNP 2001;71:i13)
  - Other helpful findings: **trauma** (c-spine, hip frx, fat embolus), **asterixis/myoclonus** (toxic, metabolic), **volume** status, **cherry red discoloration** (CO), findings c/f **toxidromes, incontinence/tongue laceration** (seizure)
- **Dx**:
  - **FSBG**, CBC/diff, BMP, LFTs, TFTs, INR, lactate, VBG, UA, EKG, CXR, bladder scan
  - Consider based on initial assessment: cultures, toxicology, drug levels, cortisol, B12, CK, CTH ± CTA head/neck, EEG, etc.

NEUROLOGIC EXAMINATION

Arousal/Mentation	Brainstem Functions	Motor Sensory
Arousal level: "AVPU scale" 1) Alert 2) Verbal stimuli 3) Painful stimuli 4) Unresponsive Orientation Attention (days of week backwards) Language: more detailed exam: comprehension, fluency, repetition, naming	Pupils (CN 2/3): - Absent light reflex (upper brainstem injury, excessive sedation) - Bilateral fixed, dilated (upper brainstem injury/compression) - Unilateral fixed, dilated (herniation w/ CN III compression) - Pinpoint (opioids, pontine injury) Blink to threat or visual field testing if able (CN 2) Corneal reflexes (CN 5/7): absent (upper brainstem injury, deep sedation), normal, or forceful closure Extraocular eye movements (CN 3/4/6): - Conjugate lateral deviation (destructive or irritative lesions) - Vertical disconjugate ("skew deviation"; structural) - Roving eyes (esp. if conjugate suggests metabolic cause) Facial symmetry (CN 7): test at rest and on activation (smile) Oculocephalic reflexes (CN 8): doll's eye movement Cough/gag (CN 9/10): if intubated, suction	Muscle strength: Observe spont. movements (e.g., symmetric? Antigravity?); if mental status allows, perform confrontational testing Sensory: compare sensation to light touch Response to noxious stimuli in each extremity: (localizing > withdrawal > extension)

APPROACH TO SUBACUTE AMS: consider Neurology consult prior to further extensive work-up

- Hx/Exam as above. **DDx** also includes: infection (HIV, Lyme, syphilis), autoimmune (paraneoplastic/anti-NMDA, sarcoid, CAPS/SLE, Sjogren's, ADEM, ALE, vasculitis), metabolic (thyroid, B1, B3, B12, Wilson's), medications, toxidromes, HTN encephalopathy, hepatic encephalopathy, PRES (tacro/cyclosporine), adrenal insufficiency/Cushings, porphyria (urine PBG)
- **Dx**:
  - **rEEG**: for non-convulsive status epilepticus (NCSE); **LTM**: for intermittent seizures
  - **MRI with contrast**: for stroke, malignancy, infxn/inflammatory process, Wernicke's
  - **LP** (CTH to r/o herniation first): see *Lumbar Puncture*, discuss advanced testing with Neurology

TREATMENT OF AMS: **diagnose and treat underlying cause**; see disease-specific pages

Nupur Goel

Neurology

Dementia

INITIAL EVALUATION: should almost always be in the outpatient setting, can assess over time without acute illness or delirium

- Obtain collateral, determine symptom onset, ADLs/IADLs, assess safety, screen for depression
- Review medications for those with cognitive SEs (e.g., analgesics, anticholinergics, psychotropic medications, sedative-hypnotics)
- Assess cognitive impairment (**MOCA >> MMSE**), track score at subsequent visits
- Labs: CBC, TSH, BMP, B12; consider: tox screen, syphilis, Lyme, HIV, UA, metals, ESR, LFT, folate, B1 (AFP 2005;71:1745)
- Imaging: NCHCT or **MRI brain (preferred)** to r/o structural lesion (tumor), assess **atrophy pattern** and vascular dementia
- Inpatient eval considered for 1) any rapidly progressing dementia syndrome (c/s Neuro to discuss LP → RT-QuIC 14-3-3 in CSF (CJD), ACE (sarcoid), autoimmune encephalitis, or 2) new dementia diagnosis in pts <55yo or with new focal deficit (eval stroke)
- **Outpt Neurology referral to Memory/Cognitive clinic** and formal neuropsychological testing

DEMENTIA SYNDROMES (Prog Neurol Psych 2012;16:11; BMJ Neurol Neurosurg Psych 2005;76:v15)

****Clinical phenotypes often overlap and may require years to differentiate****

Syndrome	Presentation	Exam	Imaging	Treatment
Gradually Progressive				
Alzheimer Dementia (60-80%, mild cognitive impairment (MCI) as precursor)	• **Short term memory loss early;** language & visuospatial deficits • Apraxia in later stages	• Nml neuro exam (excluding mental status) • Neuropsych: amnesia w/ short memory span, alexia, agraphia	Hippocampal (± global) atrophy; ventriculomegaly, ?microhemorrhages (cerebral amyloid angiopathy (CAA))	• AChE-inhibitors (mild-severe dz) • NMDA-inhibitors (mod-severe dz) • Anti-amyloid abs
Lewy Body and Parkinson's Dementia	• **Fluctuations** in attention/alertness • **Visual hallucinations (LBD)** • **REM behavior d/o** • Falls/syncope • Neuroleptic intolerance • Memory problems late	• Parkinsonism: resting tremor (can be absent), cogwheel rigidity, bradykinesia, stooped/shuffling gait • Parkinson's dementia if motor sx >1y before dementia • Neuropsych: fluctuations w/ intrusions and confabulation, visuospatial impairment	Global volume loss	• AChE-inhibitors (esp. rivastigmine) for memory sx • Carbidopa/levodopa trial for motor sx • Sx management of **autonomic dysfxn** • Avoid typical antipsychotics
Frontotemporal Dementia	***Behavioral type*** • Personality Δ (disinhib., apathy, poor insight) • Stereotyped behaviors **1° prog aphasia type** • Dysnomia, dysfluency, poor comprehension	• May have **frontal release signs** (non-specific) • 15-20% get motor neuron dz • Neuropsych testing: poor impulse control, difficulty in organization	Atrophy predominantly in **frontal and temporal lobes**	• Management of behavioral sx (consult psych) • AChE-inhibitors not helpful • **Avoid** NMDA-inhibitors
Stepwise Progressive				
Vascular Dementia	• **Abrupt focal sx, stepwise progression** • Depression common • Hx: CVA, HTN, HLD, AF	• Focal deficits (depends on stroke location), can include: weakness, dysarthria, ataxia, gait changes	Cortical or subcortical **punctate lesions, white matter disease**, and **volume-loss**	• 2° stroke prevention and RF modification • AChE-inhibitor for memory deficits
Rapidly Progressive (Ann Neurol 2008;64:97)				
Prion Diseases (Sporadic, Variant Creutzfeldt-Jacob Disease)	• **Rapidly progressive** sx in memory, concentration, judgment • Mean onset age ~60 for sporadic, 28 for variant • Younger→ ↑psych sx	• **Myoclonus, exaggerated startle response** • EPS (bradykinesia, nystagmus, ataxia), UMN (hyperreflexia, babinski, spasticity) • **LP: RT-QuIC>>14-3-3**	**MRI: cortical ribboning** on DWI, subcortical hyperintensity on FLAIR **EEG**: 1-Hz periodic epileptiform discharges	• No tx • Death w/in 1y (median disease duration 6mo)
Limbic Encephalitis (Autoimmune, Paraneoplastic)	• Sx evolve days-weeks (more indolent possible) • **Short-term memory sx** • **Psych sx:** agitation, delusions, hallucinations • **Focal seizures**	• Prominent psych features • Dyskinesias, rigidity • Autonomic instability • **LP**: lymphocytic pleocytosis, oligoclonal bands, **autoantibodies** (CSF + serum)	**MRI: FLAIR hyperintensity or contrast enhancement** (esp. in temporal lobe) **EEG**: extreme delta brush very specific	• Immunotherapy: **steroids, IVIG, PLEX,** rituximab, cyclophosphamide • **Tumor resection**

TREATMENT: can treat symptoms, but treatment does not slow the progression of disease (Lancet Neurology 2023;23:13-15)

- Inpatient Considerations:
  - For patients with Parkinson's, **do NOT stop/change** home medications (NGT if needed). Stopping sinemet can cause NMS.
  - If patient has or may have LBD, avoid antipsychotics. If necessary, atypicals (olanzapine, quetiapine) or trazadone preferred
- AChE (acetylcholinesterase) inhibitors: donepezil (first line), rivastigmine (patch), galantamine. Small effect on decreasing rate of cognitive decline, ADLs. Major side effects: GI (n/v/d); less common bradycardia and heart block (increased vagal tone)
- NMDA inhibitors: memantine. Can precipitate agitation and exacerbate neuropsychiatric sx (caution in pts with significant behavioral sx)
- Anti-amyloid Abs: In pts w/ MCI or mild dementia + amyloid (confirmed by LP or PET), aducanumab clears amyloid w/ uncertain clinical sig (Nature 2016: 537; 50-56). Lecanemab inhibits formation of AB plaques, slows decline. (NEJM 2023: 388; 9-21). Amyloid-Related Imaging Abnormalities (ARIA) (edema or hemorrhage) seen in ~20%. CMS reimburses for FDA-approved anti-amyloid abs.

Anna Bonkhoff

HEADACHES (Lancet Neurology 2023;23(1),17-19)

Approach: distinguish **primary** HA (tension, migraine, etc.) from **secondary** HA (tumor, ICH/SAH, ↑ICP, etc.)
Red Flags (consider neuro c/s or neuroimaging): new onset HA (in pt with c/f trigeminal autonomic cephalgia, hx of SCD, or >50 yo); positional or sudden+severe onset HA; headache with maximal intensity at onset, PMH immunocompromised, TB, cancer, or VPS; abn neuro exam, fever/nuchal rigidity
Tension HA: ~40% population, ♀>♂, band-like, forehead radiating to occiput, mild-mod severity, duration 30min to 7d (NRDP 2021;7,24)
Migraine HA: >3/5 "POUND" criteria (**P**ulsating, 4-72h h**O**urs, **U**nilateral, **N**ausea, **D**isabling) (JAMA 2006;296:1274)

- Migraine with aura: 1 unilateral/reversible sx [visual/retinal (scintillating scotoma, visual field deficit), sensory (tingling, numbness), speech/lang (aphasia), motor (wkness), brainstem (dysarthria, vertigo, ataxia, diplopia)] lasting minutes, usually followed by HA

ED/Inpt Management: for migraine/tension HA **w/o red flags**

Step 1
1) 1L IVF (adjust volume per comorbidities); 2) 2g Mg; 3) 1g APAP OR NSAIDs (15mg ketorolac, 500mg naproxen, 400mg ibuprofen, 25mg indomethacin); 4) 6mg sumatriptan

60 min
If not improved

Step 2
1) Chlorpromazine 25mg OR prochlorperazine 10mg OR metoclopramide 10mg; 2) Consider adding diphenhydramine 25mg

60 min
If not improved

Step 3
1) VPA 500mg IV (after negative pregnancy test); 2) Consider droperidol 2.5-5mg IV/IM OR haloperidol 5mg IM (after EKG)

Outpatient Management:

Migraine HA	
Preventatives (if >4d/mo, long duration, or disability)	**Rescue** (max 2d/w, treat early)
BB/CCB: propranolol 20mg BID up to 160mg/d; metoprolol 25mg BID up to 200mg/d; verapamil 80mg TID, ↑ gradually **Antidepressants**: amitriptyline/nortriptyline 10mg qhs, ↑ to 150mg; venlafaxine 37.5mg qd, ↑ to 75-150mg **Anticonvulsants**: topiramate 25mg qd, ↑ gradually to 100mg BID; VPA 500-1500mg qd (avoid both in young ♀) **CGRP antagonists:** erenumab 140mg monthly sc, oral atogepant (Lancet 2023;402: 775-785) **Supplements**: Mg 400mg qd, riboflavin 400mg qd, melatonin, feverfew **Botox**: referral to HA clinic	**NSAIDs/APAP** **Triptans:** sumatriptan [5-20mg q2h (max 40mg/d) intranasal, 4-6mg q1h (max 12mg/d) SC, 25-100mg q2h (max 200mg/d) PO]; zolmitriptan [5mg q2h (max 10mg/d) intranasal, 1.25-2.5mg q2h (max 10mg/d) PO]; ***C/I**: CAD/PAD*, liver dz, basilar migraine, MAOIs w/in 2w; risk of serotonin syndrome **CGRP antagonists:** ubrogepant 50-100mg q2h (max 200mg/d) PO

- Tension HA: prevention - smoking cessation, treat OSA, TCA, SSRI; rescue - NSAIDs *OR* APAP +/- antiemetic, max 2 d/w
- Menstrual migraine: before/during menstruation → NSAIDs or sumatriptan (Neurology 2008;70:1555). Consider preventive tx perimenstrually w/ slow triptan (frovatriptan) 2.5mg QD/BID (begin 2d premenstrually, for total 6d/month)
- In pregnancy: NO gadolidium contrast, NSAIDs, VPA. C/s OB/Neuro if ? re: med safety/efficacy (Continuum 2022: 28: 72-92)

VERTIGO

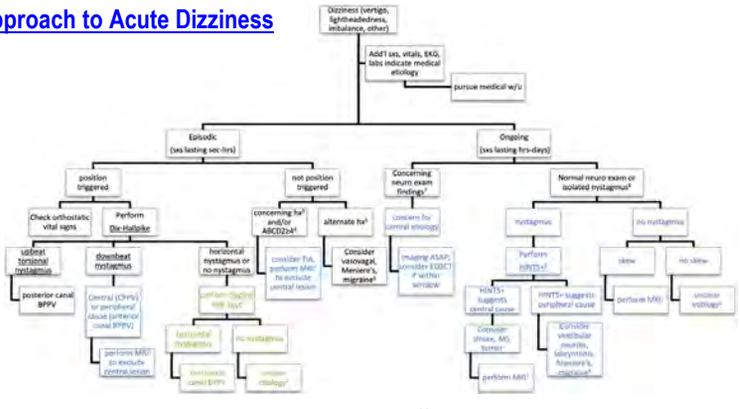
Definition: illusion of motion of self or world secondary to vestib dysfunction; a/w n/v, postural/gait instability
Approach: **distinguish central vs peripheral** (AFP 2017;95:154)

- Hx/Exam: duration of sx, episodic/persistent, triggers (position Δ), prior sx, assoc sx (5D's for brainstem: dysarthria, diplopia, dysphagia, dysphonia, dysmetria). Obtain orthostatics. Perform Dix-Hallpike. **HINTS exam video.**
- HINTS exam: each test *must be c/w peripheral to be reassuring.* In **acute, ongoing** vertigo, Sn 97%, Sp 85% for stroke (**>MRI**)
  Head **I**mpulse (pt looks at your nose, passively rotate head ~20°. No saccade = ambiguous. Catchup saccade = peripheral)
  Nystagmus (unidirectional e.g., always left-beating = peripheral; direction changing = central, any vertical = central)
  Test of **S**kew (cover one eye, then other, any vertical skew/correction = central) (Acad Em Med 2013;20:986)

Tx (peripheral): metoclopramide, prochlorperazine, meclizine (≤2w, vestib suppression), lorazepam, or diazepam, **AND vestibular PT**

	Symptoms	Ddx	Imaging
Peripheral	Severe nausea, mild imbalance, hearing loss/tinnitus	Benign positional paroxysmal vertigo (BPPV), infxn (labyrinthitis, vestibular neuritis, herpes zoster oticus), Meniere's, vestibular migraine, otosclerosis, trauma (perilymphatic fistula)	If exam reassuring, none
Central	Mild nausea, severe imbalance, rare hearing sx	Vertebrobasilar ischemia/TIA, ICH, toxic, cerebellopontine mass (vestib schwannoma, ependymoma, brainstem glioma, medulloblastoma), NF, MS, vestibular migraine	MRI brain w/ contrast (coronal DWI reformats), MRA head & neck

MGH ED Approach to Acute Dizziness



Anna Bonkhoff

ACUTE STROKE ACTIVATION (In-House Stroke Pathway)

1) If **sudden-onset focal neuro symptoms** within past 24h, activate the stroke team pager by **calling the operator at 6-3333.** This will notify the stroke resident and nursing supervisors.
2) **BE AT BEDSIDE. This a code equivalent.** Obtain 18g PIV in R AC. Place on travel monitor
3) **ABC/VS,** check **EKG**, **telemetry**, **glucose. NPO** & **HOB >30°**. **Do not treat HTN** unless BP >220/120, ACS, or ICH (see below). Confirm weight/MRI contraindications.
4) Be ready to provide the following information:
   a) **Last seen well (LSW) time.** This is NOT when symptoms were noticed but when pt was last witnessed to be normal
   b) AC or antiplatelets, CrCl, allergies, code status
   c) Contraindications to tPA/TNK **(if present, patient may be thrombectomy candidate)**
   d) Physical exam findings: most predictive findings incl. facial paresis, arm drift/weakness, and abnormal speech (JAMA 2005;293:239)
   e) Premorbid disability (e.g., walks w/ assistance, bedridden)
5) **Order STAT CTA Head/Neck** (only need to order CTA; includes NCHCT). If unable to receive contrast, stroke team may consider STAT MRI ± MRA
6) **Obtain STAT Labs**: **FSBG**, **CMP**, **CBC, PT/PTT/INR**, **type and screen**, VBG, trop, UA/UCx, tox screen, & AED levels (if appropriate), b-HCG (<50 years)
7) Neurology will perform **NIHSS** at bedside and may activate stroke group pager (pharmacy, radiology, NSGY, IR, ICU RN)

tPA/TNK Criteria

Inclusion:
1. Severe or disabling neuro deficit
2. Age ≥18
3. LSW <4.5h or 'wake-up' sx

Exclusion:
History: stroke/head trauma <3mo; head/spine surg <3mo; prior ICH; intracranial malignancy, AVM, aneurysm; incompressible arterial puncture <7d; GI onc or GIB <21d
Clinical: **BP ≥185/≥110 (treat!)**; BG <50; active internal bleeding, bleeding diathesis
Heme: plt <100K, PTT > 40s, PT > 15s; current AC (warfarin w/ INR >1.7; therapeutic heparin use w/in 48h w/ ↑PTT; DOAC w/in 48h)
Head CT: hemorrhage; large, established infarct (e.g., 1/3 MCA territory, ASPECTS <6)

Intra-arterial Therapy

Inclusion:
1. Clinical: **NIHSS ≥6, LSW ≤24h**, age 18-90, baseline mRS ≤2, life expectancy >12mo
2. Radiological: ICA or MCA M1/2 occlusion, basilar/vert occlusion, small infarct core volume

Note: *Proven* benefit w/ these inclusion crit; *probable* benefit w/ NIHSS ≥4, mRS ≤3, prox occlusion w/ ASPECTS ≥ 5. Discuss all cases w/ Neuro, may opt for IAT

Exclusion:
Anaphylaxis to contrast, acute ICH

ACUTE STROKE INITIAL MANAGEMENT (MGB GUIDELINES)

1. ISCHEMIC STROKE

IV thrombolysis: tPA or TNK: 0.25mg/kg (max 25mg); tPA given as infusion, TNK given as bolus. TNK is now preferred thrombolytic at MGB. TNK can be given by any physician.

- LSW 0-3h: goal to start IV tPA/TNK w/in 60min of ED arrival (AHA/ASA: Stroke 2018;49:e46)
- LSW 3-4.5h: IV tPA/TNK recommended but w/ relative exclusion criteria including age >80, AC (regardless of INR), NIHSS score >25, h/o both stroke & DM2 (ECASS III NEJM 2008;359:1317)
- Wake-up or Unknown Onset: consider IV tPA if DWI lesion <70mL w/o FLAIR changes (WAKE-UP NEJM 2018;379:611)

Intra-arterial therapy (thrombectomy, thrombolysis):

- Patients with disabling deficit & large vessel occlusion with **LSW <6h** (MR CLEAN NEJM 2015;372:11). May extend time to **LSW 6-24h** based on imaging criteria (DAWN NEJM 2018;378:11; DEFUSE 3 NEJM 2018;378:708)

BP control: low SBP (<150) a/w poor outcome (Arch Intern Med 2003;163:211)

- If tPA/TNK candidate: goal BP **≤185/110** prior to thrombolysis **(treat STAT if higher! 1st line: IV labetalol/nicardipine)**; goal BP **≤180/105** after TNK/tPA for 24h
- If no tPA/TNK: goal BP **≤220/120** (allow auto-regulation) for 1d; gradually reduce BP goal subsequently
- If anticoagulated: goal SBP **≤180**
- If active cardiovascular disease (ACS) & requires tighter BP control, discuss w/ neuro
- **Monitor neuro exam:** sx worse at low BP c/f ongoing ischemia → **lay bed flat, give IVF bolus, STAT page neuro**

2. HEMORRHAGIC STROKE (see *CNS Emergencies*)

Stroke Mimics: **"MINT": M**etabolic (*Gluc, Na, uremia, TME, thyroid disorders, MELAS, hypoxia, hypercarbia*), **I**nfection (*Bell's Palsy, meningitis, encephalitis, vestibular neuronitis*), **N**eurological (*migraines, Todd's paralysis/post-ictal, FND, MS, MOG, NMO*), **T**oxins/**T**rauma.

INPATIENT POST STROKE CARE

- Frequent **neuro checks** q1-2h x 24h if unstable/ICU; q4h if stable/floor pt, **STAT** head CT if change in exam
- Consult **PT, OT, SLP** (**NPO** until bedside swallow eval). Keep **euthermic** (antipyretics), **euglycemic** (FSG<180)
- Post tPA/TNK: **NCHCT 24h post-tPA** → if no e/o hemorrhagic transformation and etiology cryptogenic, start antiplatelet + DVT ppx
- If did not receive tPA/TNK: **ASA 325mg x1**, followed by long-term antiplatelet or AC (may delay antiplatelet and/or AC for large ischemic strokes). Start DVT ppx if ischemic stroke (unless large volume hemorrhagic conversion)

Work up: (see below):

- **Labs**: Acute Code Stroke labs, plus lipids, A1c, TSH, ESR, CRP, if **cryptogenic stroke**: consider RPR, HIV +/- bloodstream or CNS infectious w/u +/- hypercoagulability (d/w Neuro). (STROKE 2021;52:364)
- **Imaging**: MRI brain w/o contrast; head and neck CTA or MRA (TOF if low GFR); carotid U/S PRN
- **Cardiac**: EKG, TTE (w/ bubble if <60yo), tele then 30d MCOT vs LINQ (STROKE-AF JAMA 2021;325:2169) if tele neg for AF

CARDIOEMBOLIC STROKE

SUSPECT WHEN:

- ACA/MCA/PCA occlusion w/o sig vascular dz
- Infarcts in multiple vasc territories or cerebellar stroke
- Known risk factors (LA/LV thrombus, AF, LVEF<35%, aortic arch athero, LA dilation, R→L shunt)
- Hypercoagulability/hyperviscosity (malignancy, HbSS, cryo, clotting d/o)

DIAGNOSTIC WORKUP:

- **TTE (w/ bubble if <60yo):** if PFO, r/o venous thrombus (LENIs/ MRV pelvis), consider closure (RESPECT NEJM 2017;377:1022)
- If no hx of AF: **tele followed by 30d MCOT vs. LINQ** at d/c

ACUTE MANAGEMENT CONCERNS:

- Unless c/f hemorrhagic transformation, trans to long-term AC in 2d-14d. If concerned, delay 2-4w (d/w Neuro).

SYMPTOMATIC CAROTID STENOSIS	
SUSPECT WHEN: • Carotid stenosis present on ipsilateral side • H/o amaurosis fugax **DIAGNOSTIC WORKUP**: • **CTA** vs. **MRA** head & neck, **carotid US** typically needed prior to carotid endarterectomy (CEA)	**ACUTE MANAGEMENT CONCERNS**: • If **stroke/TIA and either stenosis >50% or high-risk plaque features,** consider revascularization (stent/angioplasty/CEA) ideally w/in 2w of sx (NASCET II NEJM 1998;339:1415) • Consider temporary **anticoagulation** (d/w neurology) • Consider **induced HTN** if symptoms fluctuate with BP
INFECTIVE ENDOCARDITIS	
SUSPECT WHEN: • Unexplained fever w/ stroke or pt with valvular dz **DIAGNOSTIC WORKUP**: • **Blood cultures, TTE** followed by **TEE** if neg • **CTA head +/- conventional angio** to identify mycotic aneurysms (↑bleeding risk)	**ACUTE MANAGEMENT CONCERNS**: • **Immediate antibiotics; tPA contraindicated** • Early cardiac surgery if small non-hemorrhagic stroke; delayed cardiac surgery (2-4w) if large or hemorrhagic stroke • **Avoid anticoagulation or antiplatelet** w/o a separate indication (**high risk** for hemorrhagic conversion and increased mortality).
CAROTID AND VERTEBRAL DISSECTIONS	
SUSPECT WHEN: • <60yo or posterior circulation stroke in pt w/o RFs • Neck pain, HA, or Horner's syndrome • Trauma (vertebral fx), chiropractor, coughing spells **DIAGNOSTIC WORKUP**: • **CTA** vs. **MRA with T1 fat saturation** • Consider connective tissue disease (Marfans/FMD)	**ACUTE MANAGEMENT CONCERNS**: • Goal of tx is to prevent stroke: highest risk in first few days • **Anticoagulation vs antiplatelet** (TREAT-CAD Lancet Neurol 2021;20:341). Prefer antiplatelet if: sx onset >3d ago, dissection extends intradurally (no AC 2/2 risk of SAH), large infarct (risk of hemorrhage) • High rate of recanalization → tx 3mo then re-image vessel
CEREBRAL VENOUS SINUS THROMBOSIS	
SUSPECT WHEN: • Positional HA, vomiting, papilledema, vision Δ • P/w seizure (common, may be difficult to control) **DIAGNOSTIC WORKUP**: • **NCHCT**: hyperdensity in torcula (dense delta sign) • **CTV** vs. **MRV** to assess intracranial venous system • Consider **hypercoagulable workup**	**ACUTE MANAGEMENT CONCERNS:** • **Immediate anticoagulation (heparin or LMWH)** even in presence of hemorrhage • AEDs if seizures (not indicated for ppx) • IV fluids, avoid dehydration, modify risk factors (smoking, OCPs) • **Long term anticoagulation (warfarin or DOAC)** for 3-6 months, then reimage (RE-SPECT CVT JAMA Neurol 2019;76:1457)

2° PREVENTION PLAN: Discuss w/ Neuro (depends on suspected etiology, size of infarct, NIHSS, ABCD², etc.). **Typically, no need** for both antiplatelet & anticoagulation for 2° stroke prevention without other indications that necessitate both

- Start **atorvastatin 80mg** with LDL goal <70 (TST NEJM 2020;382:9)
- **Antiplatelet long-term 2° prevention**
  - **ASA** 81mg qd (50-325mg/d effective; ≤200mg/d lower risk of major bleed) (Am J Cardiol 2005;95:1218)
  - **Clopidogrel** 75mg qd (may be superior to ASA for atherosclerotic vascular dz) (CAPRIE Lancet 1996;348:1329)
  - **DAPT (ASA + clopidogrel *OR* ticagrelor)**
    - **High-risk TIA (ABCD² >3) or minor stroke (NIHSS <4)**: ASA 81mg + clopidogrel 300mg load → 75mg for **3w** followed by clopidogrel or ASA alone (CHANCE NEJM 2013;369:11). May replace clopidogrel with ticagrelor (NEJM 2020; 383:207)
    - **Symptomatic intracranial stenosis**: consider ASA 325mg /clopidogrel 75mg for **3mo** → ASA 325 qD (SAMMPRIS NEJM 2011;365:993)
    - **Recurrent stroke on ASA or clopidogrel alone + significant athero**: consider DAPT long-term; however, no clear evidence & higher bleed risk (CHARISMA NEJM 2006;354:1706; MATCH Lancet 2004;364:331)
- **Anticoagulation long-term 2° prevention** (embolic infarcts from AFib, paradoxical embolus, LV thrombus, VST, or hypercoag state)
  - **Warfarin or DOAC** for pts w/ AF (start immediately for TIA, wait 2-14d for small infarct, generally 2-4w if c/f large hemispheric stroke or hemorrhagic transformation)

TRANSIENT ISCHEMIC ATTACK (TIA)

- **Definition**: *transient* neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia w/o acute infarction
- **Causes**: atherothrombotic stenosis (ICA, vertebral, basilar, small vessel), embolic (arterial, aortic, cardiac, paradoxical), dissection (ICA, vertebral) – identification will guide tx (antiplatelet therapy vs. search for underlying arrhythmia ± anticoagulation)
- **Imaging**: MRI within 24h of sx onset and vessel imaging of head and neck for large vessel occlusive disease (e.g. MRA head and neck w/ contrast [w/o contrast TOF if low GFR] vs. CTA head and neck vs. carotid ultrasound)
- **Cardiac w/u**: TTE (w/ bubble if age <60) to excl thrombus & PFO, MCOT vs. LINQ monitoring to exclude AF if suspected embolic TIA
- **ABCD²** score (**A**ge, **B**P, **C**linical features, Sx **D**uration, **D**iabetes): used to identify pts w/ high risk of ischemic stroke w/in 1w of TIA
- **Management**: immediate intervention reduces the risk of recurrent stroke (1.5-3.5% risk w/in 48h), see 2° Prevention above

POST-DISCHARGE STROKE/TIA CARE

Work up: f/u pending labs (e.g. hypercoag panel), repeat APLAS labs after 12w if pos, f/u MCOT/LINQ, order repeat imaging as noted
Management: d/c short term meds as appropriate (e.g. d/c ASA or Clopidogrel after 21d if treating per CHANCE trial); start AC per neuro (e.g. 2w after large ischemic stroke due to AF); ask about depression (Br J Psychiatry 2013;202:14), consider treating w/ fluoxetine for enhanced motor recovery (FLAME Lancet Neurol 2011;10:123); remind pts that deficits may continue to improve for >1yr, behavioral modifications (smoking cessation, diet and exercise, weight reduction), and consider sleep study if concern for OSA

INTRACRANIAL HEMORRHAGE (ICH): epidural (EDH), subdural (SDH), subarachnoid (SAH), intraparenchymal (IPH)

- **Causes**: trauma (all), ruptured aneurysm/AVM (SAH, IPH), IPH also caused by HTN, cerebral amyloid, tumor (most common w/ met breast CA, lung CA, melanoma, RCC, choroid, thyroid CAs), cortical vein/venous sinus thrombosis, hemorrhagic transformation of ischemic stroke
- **Presentation**: acute focal neuro deficit ± progressive ↓consciousness, n/v. **SAH**: thunderclap HA, N/V, meningismus; **EDH/SDH**: s/p trauma, lucid interval with EDH; **IPH**: focal neuro symptoms (may mimic ischemic stroke clinically); often with HA
- **Tests**: STAT imaging (NCHCT for all; +**CTA head if SAH/IPH**), **coags/PLTs**; **repeat CT head after 6h** to assess progression
- **STAT management**: MGH ICH Guideline
  - STAT Neurosurg (p21111) if SAH/SDH/EDH; otherwise, Neuro (inpatient: p20202; ED: p20000)
  - **Elevate HOB** to 30-45° to reduce ICP and prevent aspiration. **Obtain labs**: PT/INR, CBC, CMP, fibrinogen, type and screen
  - **BP control**: **strict SBP <140 with arterial line monitoring** (studied in SAH or ICH due to ruptured aneurysm/AVM, to prevent re-bleeding), use **IV labetalol, nicardipine, clevidipine, or esmolol** (Lancet Neurol 2008;7:391); consider less restrictive BP goal for pts presenting with SBP 180-220 (ie. target SBP <160) or 25% reduction if SBP >220 (NEJM 2016;375:1033). For aneurysmal SAH, PO nimodipine. (Stroke. 2022;53(6):1993-2005)
  - **Correct coags**: warfarin/**INR**>1.5 (vitamin K 10mg IV x1 AND 4-factor PCC/KCentra); **↓plt** (transfuse, goal >50); uremia/ antiplatelet use (consider DDAVP 0.3mcg/kg IV); heparin/LMWH (protamine sulfate); s/p tPA (check fibrinogen, give cryo, ± amicar 4-5g → 1g/hr); rivaroxaban/apixaban (andexanet alfa). **Discuss w/ neurosurg and pharm prior to reversal, consider heme consult**.
  - **Venous sinus thrombosis (VST)**: AC w/ LMWH/UFH despite ICH (Lancet 1991;338:597). Manage *seizures* (see *Seizures*) & ↑ICP.
  - Prognosis depends on age, GCS, pre-ICH cognitive impairment, and ICH volume/location (FUNC Score; Stroke 2008;39:2304)
  - Typically, acceptable to restart DVT ppx in smaller hemorrhages **48h after** last stable NCHCT, confirm w/ Neurology
  - Start prophylactic levetiracetam 500mg BID **x7d** for traumatic SDH or SAH (Neurocrit Care 2010;12:165)

ELEVATED INTRACRANIAL PRESSURE (ICP)/HERNIATION: ICP > 20mmHg

- **Etiologies**: mass (tumor, abscess, hemorrhage), cerebral edema (infarction, inflammation, hyperammonemia, DKA), hydrocephalus (tumor, intraventricular hemorrhage, leptomeningeal disease, meningitis), PRES, VST. High ICP may cause compression/ischemia. Severe local swelling or CSF drainage with large space-occupying lesions causes herniation (displacement & compression of brain).
- **Signs of ICP**: nausea, vomiting, headache, diplopia somnolence/confusion, or limited upgaze; flexor/extensor posturing; ipsilateral hemiparesis (uncal herniation); **fixed/dilated/asymmetric pupil, Cushing's triad (bradycardia, ↑SBP, irreg. breathing)**
- **Tests**: STAT head CT, blood gas, BMP, CBC
- **Management**: MGH ICP Guideline
  - STAT Neurosurgery for ICP monitor/EVD placement/decompressive hemicraniectomy, Neurology to discuss need for Neuro ICU
  - Secure ABCs, elevate HOB to 30-45˚, keep head midline (to secure venous drainage), treat pain/agitation, maintain BP to avoid CPP <50mmHg (CPP=MAP-ICP).
  - If c/f herniation, **hyper**ventilate to PaCO2 ~ 30-35 mmHg (transiently reduces ICP)
  - **Hyperosmolar therapy**: **Check BMP, Sosm q6h**. **Start with 23% saline boluses**, then use mannitol, or both staggered 3h apart (discuss with Neuro) (Emerg Med J 2014;31(8):679-83)
    - 23% saline 30cc q6h (requires central line → better option for patients with AKI/CKD, use with caution in HF)
      - Hold if Na >160
    - IV mannitol therapy 1g/kg q6h (max 100g, use with caution in pts on HD). **Hold** if osm gap >10, Na >160, serum osm >340
  - **If edema 2° to malignancy or bacterial infection**, give 10mg IV dexamethasone x1, then 4-8mg BID
  - **Complications during LP**: **if sx of herniation or opening pressures >40cm H_2O with space occupying lesion**, consider STAT head CT. Immediately replace stylet into needle, only drain CSF from manometer, STAT Neurosurgery consult.
  - **Do not** use **hypo**tonic solutions for resuscitation (i.e. LR) as this can worsen edema. Use 0.9% NaCl (NS) instead. J Neurosurg 1995;83(6):949-62).

HYPERTENSIVE ENCEPHALOPATHY: PRES (posterior reversible encephalopathy syndrome)

- Dx of exclusion w/ (sub)acute onsed, varied neuro sx, vasogenic edema, & severely elevated BP. (J Neurol 2017; 264(8): 1608–16).
- **Typically associated with**: severe HTN, but also relative HTN in setting of eclampsia/pre-eclampsia, cytotoxic/immunosuppr meds (cyclosporine, tacro, cisplatin, bevacizumab), acute/chronic renal failure, uremia, sepsis, vasculitides, TTP → due to impaired cerebral autoregulation and endothelial dysfunction, hypoMg (NEJM 1996;334:494)
- **Symptoms**: thunderclap HA, confusion, decreased consciousness, visual disturbances, seizures, ICH and ↑ICP
- **Tests**: **MRI brain w/ contrast**: FLAIR w vasogenic edema w/in white matter in the posterior cerebral hemispheres; DWI/ADC typically nl (though can have strokes); additional regions can be affected incl. brainstem, cerebellum, basal ganglia, frontal lobes
- **Management**: ICU if severe, strict BP control (goal SBP <140, reduce by 210-15% 1st hour then 5% daily, if severe use nicardipine or labetalol drip), treat seizures, Mg^{2+} (esp. in eclampsia), remove inciting factor (i.e stop medication, dialyze if needed, treat infx)
- **Prognosis**: often fully reversible; complications include progressive cerebral edema, ICH, stroke, death

CORD COMPRESSION: high level of suspicion in cancer or injection drug use patients with back pain, urinary sx or LE weakness

- **Etiologies**: subacute (tumor/mets, abscesses) vs acute (disc herniation, trauma, hemorrhage)
- **Symptoms**: back pain (worse at night/Valsalva), motor weakness, **hyper**reflexia below lesion if chronic (**hypo**reflexic if acute, cauda equina), ⊕Babinski, loss of sensation ("sensory level"), bowel/bladder incontinence OR retention, loss rectal tone, saddle anesthesia
- **Imaging**: **STAT MRI C/T/L w/ contrast** (cord compression protocol), call ED (x63050) or inpt MRI (x64226) to prioritize
- **STAT page** NSGY/Ortho spine for decompression ± Rad Onc for possible XRT if tumor related (see *Oncologic Emergencies*)
- **Dexamethasone**: 10mg IV x1 then 4mg IV Q6H, esp in malignancy (Cochrane Database Syst Rev. 2015 Sep 4;2015(9):CD006716)

Neurology

Seizures

DEFINITIONS Epilepsia 2017;58:522 Continuum 2019;25:306 Continuum 2022;28:230 Lancet Neurology 2023;23:19

- **Classification of seizure (sz)**: describe onset and semiology
  - *Focal onset:* **unilateral**, occurring in one hemisphere, ± impaired awareness, may evolve to bilateral tonic-clonic
  - *Generalized onset:* occurring in & rapidly engaging bilateral distributed networks, **impaired awareness**
  - *Motor:* limb stiffening (tonic), limb jerking (clonic), brief muscle contraction (myotonic), loss of tone (atonic), or automatisms
  - *Non-motor:* autonomic changes, staring/behavioral changes, cognitive changes, sensory phenomena
- **Epilepsy**: ≥2 unprovoked sz >24h apart or 1 unprovoked sz + recurrence risk ≥60% over the next 10y or dx of an epilepsy syndrome
- **Status epilepticus**: ≥ 5min of continuous sz or 2+ sz w/ incomplete recovery of consciousness in between (Epilepsia 2015;56:1515)
- **Non-convulsive status epilepticus**: electrographic sz ≥10s or EEG & clinical improvement w/ tx (Epilepsy Behav 2015;49:158)
- **Psychogenic non-epileptic sz (PNES)**: most prevalent phenotype of fxnl neuro disorder (FND). Long & fluctuating course, asynchronous/side-to-side mvmts, closed eyes, preserved awareness, memory of spell. No pathology. changes in brain physiology.

ETIOLOGY: provoked vs unprovoked?

- **Causes/RFs**: primary epilepsy, vascular (ischemia/hemorrhage), withdrawal (EtOH/BZD), masses (tumor, abscess), trauma, metabolic (↓BG, ↑CO2, ↓O2, ↓Ca, ↓/↑Na), meds, infxn (systemic, CNS), HTN/HoTN, high fever, eclampsia, PRES
- **Ddx**: syncope, TIA, migraine, PNES (~30% have epilepsy, Brain Behav 2022;12), myoclonus, dystonia, cataplexy, tremor, catatonia
- **H&P**: sz history, prodrome (headache, confusion, anxiety, irritability), med list (↓sz threshold, e.g. penicillins, opioids, antipsychotics), triggers (exertion, pain, fatigue, stress, cough, urination/defecation, infxn), tongue biting (lateral), incontinence, lateralizing signs, EtOH/BZD. GET COLLATERAL.
- **Labs**: **FSBG, Utox & Stox, UA, CXR, AED lvls, BMP/Na**, Mg/Phos, CBC, LFT, VBG, CK, INR, lactate, b-hCG. Prolactin less helpful.
- **Monitoring**: tele (↑risk for ictal bradycardia/aystole), pulse O2 (NEJM 2013;368:2304-12)
- **Neuroimaging**: epilepsy protocol MRI w/ contrast for **unprovoked 1st sz** (Continuum 2022;28(2 Epilepsy):230-260), **focal seizure,** focal neuro exam, h/o trauma, malignancy, or HIV. 10% found to have relevant structural lesion (Neuro 2007;69:1996).
- **LP/BCx**: if febrile, HIV/immunocompromised, 2° autoimmune encephalitis (anti-NMDA) (Epilepsia 2020;61:1341)
- **EEG**: within 24-48h if not seizing, **emergent if seizing**. **DO NOT wait for EEG to manage**. If emergent, contact EEG fellow (p16834).

SEIZURE PPX Neuro 2015;84:1705 Neuro 2006;67:s45 Cochrane 2008;CD004424 Neurosurg Focus 2008;25:E3 Stroke 2016;47:2666

- **No AED in 1st sz unless** prior TBI, abnml EEG, or abnml imaging. Early AED ↓short term recurrence (<2y), not remission (3+y).
- **ETOH seizure**: ppx **not indicated** for intox/withdrawal, **ICH**: only if clinical sz or traumatic etiology, levetiracetam 500mg BID x7d
- **Brain tumor**: no ppx. If sz, levetiracetam > lacosamide (fewer chemo interactions), **Severe TBI**: levetiracetam 500-750mg BID x7d
- **PNES**: Outpatient, CBT & Psychiatry. Inpatient, educate about functional neurological sx, c/s social work.
- In MA, **no driving** (for LOC event) until 6mo event free. Counsel pt, include in d/c summary. Restrictions vary by state.

TREATMENT

- Seizures that are **NOT status epilepticus**: tx if a) GTC > 2-3min or b) patient has several focal seizures within 24h ("clustering")
  - **Lorazepam 1-2mg IV** (1mg if elderly or low weight), can repeat x1 if needed. Then discuss possible ASM load with Neurology.
- Treatment of **status epilepticus** (MGH Status Epilepticus Protocol)
  - **Lorazepam 4mg IV q5min x1-2** and order 2nd line agent → persists >5min→ **call Neurology,** give 2nd line agent: **levetiracetam 60mg/kg x1 (max 4500mg/dose)** vs. valproate 40mg/kg x1 (max 3000mg/dose) vs. fosphenytoin 20 PE/kg (over 10 min) → persists >20min → intubation w/ propofol/midazolam/(3rd-line) ketamine. Avoid etomidate. (NEJM 2019;381:2103).
  - If no IV access, **midaz 10mg IM**/nasal/buccal or diazepam 20mg PR. 2nd line medications require PIV.
- Suspected preeclamptic seizure: 4mg IV Mg x1, consider mag sulfate infusion (2g/h), and call OBGYN

AED	Loading	Dosing	Goal Level	Side Effects
Levetiracetam (Keppra)*	40-60mg/kg Max 4.5g	1:1 PO:IV	No goal, level to check adherence	**Psych** (aggression, anxiety/depression, psychosis)
Valproic acid (Depakote)†	20-40mg/kg Max 3g	1:1 PO:IV	50-100mcg/mL (>1h post load)	↑**weight**, **hepatitis, N/V**, tremor, alopecia, encephalopathy (↑NH3), ↓platelets. **Good w co-morbid mood disorder.**
Phenytoin (Dilantin)†, Fosphenytoin†	20 mg/kg Max 1.5g	1:1 PO:IV	10-20mcg/mL, correct for alb, (2h post load)	**HoTN/arrhythmia** (if run >50mg/min; fosphen. has ↓cardiotox), gingival hypertrophy, nystagmus/ataxia/slurred speech, blood dyscrasia, DRESS, **rash (TEN/SJS)**
Lacosamide (Vimpat)	200-400mg	1:1 PO:IV	10-20mcg/mL	HA, diplopia, dizziness, ataxia, nausea. Get EKG before & after load (**PR prolongation, flutter/fib**).
Lamotrigine (Lamictal)*	No Load	Only PO	3-15mcg/mL	**Rash (TEN/SJS)**, DRESS, nausea, drowsiness, ↓PMNs, HLH, aseptic mening. **Good w co-morbid mood disorder.**
Topiramate (Topamax)†	No Load	Only PO	N/A	↓**weight**, **drowsiness**, glaucoma, NAGMA→nephrolith., cognitive dysfxn, aggression, anxiety/depression
Carbamazepine (Tegretol)	No Load	Only PO	4-12mcg/mL	SIADH, N/V blood dyscrasia, ataxia, blurred vision, DRESS. Screen for **HLA-B*1502** if Asian descent for **↑risk of TEN/SJS** (Epilepsia 2019;60:1472).
Clobazam (ONFI)	No Load	1:1 PO:SUSP	N/A	**Drowsiness**, resp. depression (BZD), ataxia, URI, fever
Perampanel (Fycompa)	No Load	1:1 PO:IV	N/A	**Aggression/irritability**, dizziness, drowsiness, weight gain

Others: Brivaracetam, Cenobamate (effective in highly active & ultra-refractory focal epilepsy; Epilepsia 2023;64:1225-35), Ethosuximide (absence), Phenobarbital (historical), Vigabatrin, Zonsiamide. Aerosolised alprazolam as rescue medication (Epilepsia 2023;64:374-85).

**Preferred in pregnancy, †Teratogenic*

Neurology Weakness & Neuromuscular Disease

CHARACTERIZATION OF A PERIPHERAL PROCESS

- Weakness: ask about **function** (rising from a chair, stairs, brushing hair, tripping while walking, opening jars, zippers/buttons) and onset/tempo. Clarify vs. generalized fatigue or systemic symptoms (i.e. of anemia, infection, electrolyte abnormalities, thyroid/adrenal issues)
- **UMN signs**: spasticity, increased tone, hyperreflexia, ⊕ Babinski; **LMN signs**: fasciculations, atrophy, decreased tone, hyporeflexia
- **Patterns**: UMN (UE extensors, LE flexors), LMN (length dpdnt, myotomal), myopathy (proximal), bulbar (dysphagia, dyspnea, dysarth.)
- **Sensory sx**: negative (↓ temp/pin (small fibers), vibration/proprio (large fibers), imbalance) or positive (tingling, allodynia, hyperalgesia)
- **Autonomic sx**: orthostasis, constipation, urinary retention, sexual dysfxn, changes in sweating, post-prandial nausea or early satiety
- **Exam**: 0/5 - no mvmt, 1/5 - flicker, 2/5 - mvmt if no gravity, 3/5 - mvmt vs. gravity only, 4/5 - dec. power vs. resistance, 5/5 - nml
- **EMG/NCS**: localization (radicular, nerve, junction, muscle), motor vs. sensory, axonal vs. demyel (guides tx), severity (guides prognosis). **Higher yield if sx for ≥2-3w (do as outpatient).**

Localization	Associated Signs/Sx	Diagnostics	Important/Common Causes
Brain	Cortical (lang., visual field, neglect), cerebellar, UMN	**MRI Brain** (with contrast if c/f cancer, infection, demyelinating dz)	**Vascular** (hemorrhage, ischemia)**, tumor, trauma,** demyelinating dz
Spinal Cord	Truncal sensory level, bowel/bladder dysfxn, UMN (if chronic)	**MRI Spine** (level from exam, contrast if c/f cancer, infxn, demyelinating dz); **CSF** if c/f inflammatory or infxn	**Transverse myelitis** (MS, NMO, sarc/Sjo/SLE), infxn (viral myelitis, abscess, TB, AIDS, HTLV, syph.), paraneop, neoplasm, **↓B12/Cu**, vascular, **trauma,** toxic, myelopathy
Anterior Horn Cell	LMN; if motor neuron dz, UMN & LMN	**NCS/EMG** ± MRI brain and spine	**ALS,** SMA, poliomyelitis, acute flaccid myelitis
Radicular	Motor/sensory corresponding to nerve root. Radiating pain.	**MRI Spine** (nerve root from exam) **LP** if polyradiculopathy **NCS/EMG** can aid in localization if sx >3w	Nerve root compression 2/2 disc hernation, spondylosis; polyradiculopathy→DM (thoracic, lumbosacral), AIDP/CIDP, infxn (Lyme, HIV, CMV), malignancy (leptomeningeal, chemo)
Peripheral Neuropathy	Motor/sensory; autonomic dysfxn. Often symmetric/ length dependent.	**Labs**: A1c, B12/MMA, S/UPEP **Consider**: Lyme, syphilis, HIV, B1, B6, vit E, B3, Cu, ANCA, ANA, ESR, CRP, RF, TSH, C3/C4, celiac w/u **NCS/EMG**: localization & pattern (not for eval of small fiber dz)	Symmetric, length dependent: toxic/ metabolic/nutritional (DM, chemo, EtOH, ↓B12, critical illness), hereditary (CMT), **AIDP/CIDP**, paraprotein-related Mononeuropathy: compression/trauma Multiple mononeuropathy: **vasculitis**, DM, amyloid, RA/SLE/sarcoid/Sjogren, leprosy
NM Junction	Motor only; weakness fluctuates with use; a/w ptosis, diplopia.	**Ice pack test** **Labs**: MG panel (below) **NCS/EMG**: repetitive stim, single fiber EMG**. CT chest** if above c/w MG	**Myasthenia gravis**, Lambert-Eaton, botulism, tick paralysis, meds (imm checkpt inhib, penicillamine, aminoglycosides), snake/spider venom
Myopathy	Proximal weakness most common. Pain uncommon.	**Initial labs**: CK/aldolase, LDH, LFTs, TSH/fT4, PTH, ESR/CRP **EMG**: e/o muscle irritability, chronicity **May need muscle biopsy**	**Critical illness**, meds (**steroids**, **statins**, colchicine, cyclosporine, NRTI), **inflammatory** (inclusion body, dermatomyositis, polymyositis)

Sx tx: Pain: gabapentin, pregab, TCA, SNRI; Dysautonomia: compress. hose, abd binder, fludrocort, midodrine, droxidopa, pyridostigmine

ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (GUILLAIN-BARRÉ SX)

- **Symmetric, progressive** numbness & weakness, **hypo/areflexia**, ±bulbar weakness, autonomic dysfxn, **acute resp failure (10-30%)**
- Causes: recent infxn (*Campylobacter*, HIV, COVID, CMV, EBV, *Zika*), vaccine (rare), meds (TNF-alpha antag, tacro, imm checkpt inhib)
- Dx: **LP** w/ albuminocytologic dissociation (↑protein, nml WBC), **NCS/EMG (2-4 wks after symptom onset), RT consult for mechanics**
- Tx: IVIG or plasmapheresis; monitor resp with NIF/VC (RT); glucocorticoids not effective
- **Elective intubation 20-30-40 Rule**: VC <20mL/kg, NIF weaker than -30cm H2O, MEF <40cm H2O, or ≥20% decline in ~24h
- Mimics: CIPD, myelopathy, trans. myelitis, ALS, polio, myositis, tick paralysis, vasculitis, paraneop, toxin/vit def, hexacarbon expos., AIP
- **AIDP less likely**: persistent asymmetric weakness, bowel/bladder dysfxn at onset, >50 CSF PMN, sensory lvl, severe pulm dysfxn w/o limb weakness at onset, fever at onset, nadir of weakness in <24h or >4w, purely sensory

MYASTHENIA GRAVIS/LAMBERT EATON (MG/LEMS)

- Weakness of voluntary muscles. MG: **worse w exertion**, repetitive mvmts, & in the evening. LEMS: transient improvement w activity.
- Typically involves ocular (ptosis, diplopia), bulbar, respiratory, neck, proximal>distal limb muscles
- Cause: auto-Ab against postsynaptic ACh-R in skeletal muscle (MG) or voltage-gated calcium channels (LEMS); **ICI therapy.**
- Exam: **ptosis w up-gaze** after 1min. Ice pack test: after observing ptosis, place ice on eyes for 1min, ptosis will improve. Fatiguable diplopia. (Historical: tensilon test, requires atropine at the bedside. Only improves MG not LEMS).
- **Monitor for respiratory failure**: track number counting in single breath, worry if <20, assess cough/swallow. Trend mechanics with RT: NIFs/VC as above (*20-30-40 Rule*). Aggressive pulm toilet. HOLD pyridostigmine if bulbar sx and/or intubated (2/2 ↑secretions)
- Dx: **Ach-R Ab** (80-90% seropositive in generalized dz, 40% in ocular dz, ~100% sp); if ⊖, check anti-MuSK. **EMG/NCS** w **repetitive stim**: decremental response (MG) or potentiation (LEMS). **Chest CT**: r/o thymoma. Find **underlying malignancy** in LEMS.
- Tx: sx (pyridostigmine); immune: rapid (IVIG, plasmapheresis), chronic (steroids ±AZA/MMF); thymectomy (thymomatous MG or <65yo)
- **Myasthenic crisis:** exacerbation requiring intubation or noninvasive vent. Triggers include surg, infxn, pregnancy, **meds** (abx incl FQs, macrolides, AGs; AEDs; antipsychotics, BBs, CCBs, Mg, iodinated contrast rarely). AVOID succinylcholine.

Neurology

Neuroprognostication

Neurological prognostication refers to the recovery from a consciousness disorder after severe brain injury; Neuroprognostication is critical, complex and uncertain (Semin Neurol 2017;37:40). The introduction of targeted temperature management (**TTM**: see *Cardiac Arrest & TTM*) can alter the timeframe for neurological recovery and the interpretation of prognostic markers. It is important to use the following as a framework to conceptualize neuroprognositication in conjunction with active GOC conversations and close interactions with Neurology.

Cerebral Performance Category (CPC)

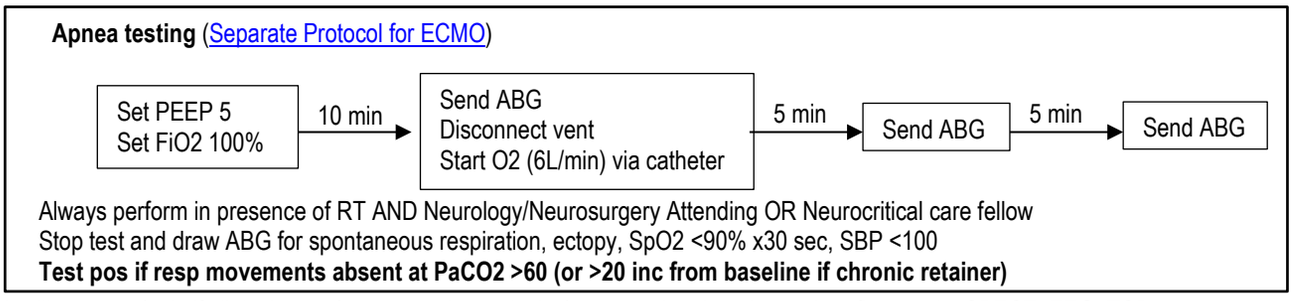
- Original CPC scale (NEJM 1986;314(7):397-403) is commonly used, though does not always reflect patient/family values (Resusc 2016;100:6-10)
- Good Outcome:
  - CPC 1. Able to work. May have mild neurologic/psychologic deficits.
  - CPC 2. Moderate deficits. Capable of independent activities of daily life. Able to work in sheltered environment
- Poor Outcome:
  - CPC 3. Severe deficits. Conscious but dependent on others. Ranges from ambulatory to severe dementia/paralysis
  - CPC 4. Coma (no wakefulness) or vegetative state (wakefulness but unawareness)
  - CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

Post-Cardiac Arrest Diagnostics

- **Critical Caveat:** each of the below tests has a FPR > 0 (i.e. will be "positive" for prediction of poor outcome in some patients who would have a good outcome); FPRs are likely underestimated due to "self-fulfilling prophecy" bias; use of prognostic indicators in combination may reduce FPRs and withdrawal of life sustaining treatment in patients who otherwise would have had a good outcome (MGH Neuroprognostication Guidelines)
- Clinical exam
  - Poor prognosis: **status myoclonus** (spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs, axial musculature ± EEG correlate) < 48h post arrest or rewarming. **Absent brainstem reflexes** (esp. bilateral pupillary/corneal) 3-7d post arrest or rewarming.
- Electroencephalography (EEG): started immediately post arrest, continued for 24h post rewarming
  - Poor prognosis: absence of EEG reactivity, seizures/status, discharges, voltage attenuation, alpha or delta coma patterns, burst suppression (Neurology 2013;80:339)
- Neuron specific enolase (NSE): check serially at 24, 48, 72h post arrest
  - Non-specific marker of neuronal injury (also found in RBC and platelets)
  - Poor prognosis: >70mcg/L at 24-48h, >59mcg/L at 48-72h (Neurology 2022;98:e62)
- Somatosensory evoked potentials (SSEP): 48h post cardiac arrest or rewarming
  - Measurement of brain activity in response to somatosensory stimulation
  - Poor prognosis: bilateral absence of N20, which reflects the integrity of thalamocortical projections
- CT head: 48h post cardiac arrest or rewarming
  - Poor prognosis: widespread hypodensity in combination with poor clinical exam
- Brain MRI: 2-6d post cardiac arrest or rewarming (not useful < 48h post arrest/rewarming)
  - Poor prognosis: extensive restriction of diffusion in combination with other poor prognostic signs

Brain Death

- Variability exists in prerequisites, clinical evaluation, apnea/ancillary testing to evaluate for brain death across hospitals.
- Prerequisites: irreversible CNS catastrophe; absence of severe acid-base, electrolyte, or endocrine abnormality; neg tox screen, clearance of CNS depressants (i.e., 5 half-lives since last dose or subtherapeutic level), absence of neuromusc blockade, eucapnia, euvolemia
- In principle, brain death = **coma** + **absence of brainstem reflexes** + **apnea** with irreversible etiology (NEJM 2021;385:2554-61)
- **Death by neuro criteria confirmed when all prerequisites met PLUS**
  - Consistent coma and brainstem reflex exams and positive apnea test OR
  - Incomplete brainstem reflex exams due to patient factors, positive apnea test, and one supporting ancillary test OR
  - Consistent coma and brainstem reflex exam, inconclusive/aborted apnea test, and one supporting ancillary test
- Clinical exam (by Neuro/NSGY attending or Neurocrit care fellow): coma exam (i.e. absence of response to nox stim in extremities & head (incl. absence of decorticate/decerebrate posturing), absent brainstem reflexes (pupils, oculocephalic [doll's eyes], VORs [cold calorics], corneals, cough, gag)



- Ancillary tests (only if clinical exam/apnea test inconclusive): conventional angio, nuclear flow study, SPECT, EEG, TCDs
  - For EEG, order evoked potentials and ensure electrodes are tested (touched) at beginning of epoch (ask techs)

THREE ELEMENTS OF VALID INFORMED CONSENT (Psychosomatics 1997;38:119; NEJM 2007;357:1834)

1. Relevant clinical information: at minimum: diagnosis, proposed intervention, its purpose, its basic risks/benefits, alternatives, and risks/benefits of alternatives (including no intervention)
2. Voluntary decision: decision is voluntary and w/o coercion from hospital staff or family/friends (advice/discussion are NOT coercion)
3. Capacity: confirm patient is able to make a decision about the ***specific question*** being addressed at the time it is being asked

EXCEPTIONS TO INFORMED CONSENT

1. Emergency in incapacitated patient: imminent risk of death or serious harm without medical intervention. All attempts should be made to find HCP/other surrogate decision-maker. Always discuss with team attending. Document emergent situation, lack of capacity, lack of available surrogate, need for emergent intervention. Consider 2nd opinion/consulting MGH lawyer-on-call (p26831) if time allows. If not, need to make a team-based clinical judgment of emergency.
2. Lack of capacity or competency: turn to the appropriate HCP/surrogate decision-maker; note **only a court-appointed surrogate can override an incapacitated patient's verbal refusal** or physical resistance in a non-emergency situation

CAPACITY ASSESSMENT

- **Capacity**: person's ability to make an informed decision about a ***specific question***. It **can change over time**
- **Competence**: legal designation made by a judge. When deemed lacking, the judge may make a global determination or define time and domain-based parameters within which a legally appointed surrogate can make decisions on the patient's behalf.
- **Any physician can make a determination of capacity**. Psychiatry should be consulted only for complex cases (i.e neuropsychiatric illness impairing decision-making, disagreement between patient/family/medical team.) Be ready to tell consult: Specific decision the pt is asked to make, the decision pt offers, risk/benefit of intervention. Be prepared to accompany consultant during evaluation if needed to provide info to pt re: proposed dx test/tx/intervention
- **The strictness of the capacity test varies as the risk/benefit ratio of a decision changes**: the more favorable the risk/benefit ratio, the lower the standard for capacity to consent and higher the standard to refuse, and vice versa

CRITERIA FOR DETERMINING CAPACITY (ALL must be met for pt to have capacity) (NEJM 2007;357:1834; NEJM 1988;319:1635)

Criterion	Approach in Physician's Assessment
Communicate a clear and consistent choice	Ask pt to indicate a choice. Inability to express one or to participate in assessment is equivalent to incapacity in a sufficiently high stakes situation. Frequent reversals of choice may also indicate lack of capacity.
Understand relevant information	Ask pt to describe understanding of the information given by the physician (dx, proposed intervention, purpose, risks/benefits, risks/benefits of alternatives including no intervention). Some cueing is OK here. Do not overestimate what is reasonable to expect from a lay person.
Appreciate the situation and its consequences	Ask pt to describe views of diagnosis, interventions, and likely outcomes. Is patient aware of their illness? Its seriousness? Consequences? What are the patient's non-medical priorities that factor into their decision?
Able to manipulate info in a rational fashion	Ask patient to compare treatment options, consequences, and reasons for choice. Does the patient weigh the risks and benefits logically? A rational choice may not be the same as a "good" one.

SURROGATE DECISION-MAKERS

- Encourage each pt to sign legal HCP form specifying surrogate. "Confirmed" (by court procedure) when pt lacks capacity and retains ability to refuse/resist medical activities. Confirmation of HCP is not needed if pt is incapable but agreeing, assenting, or unconscious.
- Surrogate's job is, ideally, to make the decision pt would have made for themself if able — **not** what the surrogate wants. If a pt's wishes cannot be known, the surrogate should make the decision in the "best interests" of the patient
- HCP may be unconfirmed (most common) or confirmed. **Court-confirmed HCP is required when pt's surrogate is activated & pt actively objects to surrogate's decision**. If HCP confirmation required, contact MGH Guardianship team
- Guardianship: legal process where MA Probate Court grants a guardian the authority to make decisions on behalf of someone who a judge has ruled is not competent. **Required when there is no HCP identified & pt is unable to designate a HCP**. *Note: a patient may not have capacity to make a certain medical decision **and** still have capacity to designate a HCP*. For help: 'Guardianship Team'
- Emergency guardianship is not required to provide lifesaving treatment & should not delay care (see above).

TEMPORARY INVOLUNTARY (PSYCHIATRIC) HOLD (Section 12 in MA - MGL ch.123 §12): consult Psychiatry for all on 12a

- **Section 12a** (the front of the "pink paper"): MD, NP, psych RN, psychologist, SW, or police officer uses to apply for involuntary psych eval and possible hospitalization of pt who, based on MD's exam & opinion, requires hospitalization to avoid likelihood of serious harm by reason of primary mental illness. Authorizes transport to psych facility and, if necessary, restraint of the pt to maintain safety
- Issued when likelihood of serious harm to self and/or others is imminent (within 24-72h) AND:
  1. Is the result of a "**serious mental illness**": must be supported in writing with specific evidence. **Symptoms caused solely by *intoxication, withdrawl, delirium, dementia, or intellectual disability* do not constitute a serious mental illness**
  2. Meets ≥1 of the following 3 criteria: (1) substantial risk of **physical self-harm**; (2) substantial risk of **physical harm to others**; (3) very substantial risk of **physical self-impairment or injury** as manifested by evidence that the person's judgment is so affected **(i.e., by serious mental illness)** that they unable to protect themself in the community.
- **Section 12b** (reverse side of the "pink paper,"): completed by evaluating psychiatrist, authorizing involuntary psych hospitalization

SAFETY (MEDICAL) HOLD (PATIENTS LEAVING AMA POLICY)

- Order that can be placed that empowers staff to prevent pt from leave AMA when the following criteria are met: (1) Patient lacks capacity to leave the hospital and is attempting to do so (2) There is imminent risk of harm to self and/or others from leaving AMA (3) Pt does not meet S12 criteria (4) Physical restraint or chemical tranquilization would be excessive
- Staff may prevent a pt under a safety hold from leaving AMA using non-physical methods (e.g. verbal redirection, standing in a doorway or exit, preventing an elevator door from closing) but should not place themselves at risk or physically hold a patient.
- If the pt should escalate or become physically aggressive, then providers should follow restraint/seclusion protocols

AGITATION MANAGEMENT 101

- Goals: 1) Safety of pt & staff, 2) Help pt manage distress (promote calm, not put pt to sleep or punish) 3) Avoid restraints as able
- General Considerations:
  - Take notice early of anger/fear, yelling, pacing/restlessness, sweating, aggressive body language. LISTEN to RN and PCA concerns
  - Address any easily/quickly reversible issues: hunger, thirst, pain, communication breakdowns. Consider urinary retention, & constipation as sources of discomfort, particularly in patients who are nonverbal, have ASD, or neurocognitive disorders. Work up/treat any other contributors (delirium, psych d/o, substance intox/withdrawal).
  - Offer PO medications early in escalation process. Think about standing medication if recurrent concerns.
  - If pt requires restraints, should **always** receive med to help ease/lessen time in restraints. Monitor for ongoing need and discontinue restraints ASAP. Restrained pts are at risk of aspiration, rhabdomyolysis, MSK injury, delirium. **Restraints/seclusion may be traumatizing, are associated with morbidity/mortality, and are the result of treatment failures. Any restraint episode warrants reassessment of treatment approach.**

APPROACH TO VERBAL DE-ESCALATION: DEFUSE (NUEMBLOG)

Decide if pt is appropriate for verbal de-escalation. Clues include a patient who is responsive, engageable, not an active threat to safety.
Ensure safety. Ensure adequate backup. Clear area of potential weapons (loose objects, supplies). Respect personal space (two arm's length between you and patient)
Form relationship. Introduce yourself by name and title. Ask what they like to be called. If they are responsive in conversation, consider asking, "Will you allow us to help?". Use short sentences and simple vocabulary.
Utilize interests. Identify patient's wants and feelings. Agree as much as possible, either in truth, principle, odds, or to disagree. Reinforce that you will let no harm come to patient.
Set limits. Speak matter-of-factly about consequences for bad behavior. Offer choices for behavior, even if it's between oral or IV meds. Use repetition as needed until you are heard by patient.
Enforce/Evaluate. If aggression escalates and violence seems imminent, withdraw and mobilize help. Once situation defused, by either verbal de-escalation or medication, debrief staff and/or patient.

CHOOSING MEDICATIONS – CHART REVIEW:

- Consider current standing medications. Can any of these be used for acute agitation?
- Allergies/adverse reactions
- Major medical comorbidities (heart conditions, h/o arrhythmia, OSA, COPD, Parkinson disease, fall risk)
- MAR: previous medications for agitation, medication burden (is patient near max daily dose for an agitation medication?)
- QTc: if high overall load of QTc-prolonging medications or underlying heart disease, consider options with less QTc-prolonging potential. If no recent EKG, do not defer giving meds to obtain one– you can plan to obtain when next able.

MEDICATION OPTIONS AND SPECIAL POPULATIONS: *always offer PO option first if pt able to safely take PO*

- General principle: Treat exacerbations of the underlying condition with the agent intended for it, within medical reason:
  - GABA withdrawal, catatonia, stimulant intoxication → benzodiazepines
  - Psychosis → antipsychotics
  - Mania → antipsychotics/mood stabilizers/benzodiazepines
  - AVOID antipsychotics in patients with catatonia and NMS
- Medication options: (MDD = Max Daily Dose, ODT = Oral Disintegrating Tablet)
  - Consider consulting psychiatry for pts requiring IM meds
  - **Quetiapine** (PO) 12.5-100mg. Can lead to orthostatic hypotension.
  - **Trazodone** (PO) 12.5-100mg. Good for elderly; no cardiac or delirium risks.
  - **Olanzapine** (PO, ODT, IM, IV) 2.5-10mg. MDD 20mg. NOTE: **do not** co-administer parenteral benzos with parenteral olanzapine within 4 hours (risk of lethal respiratory depression)
  - **Haloperidol** (PO, IM, IV) 2.5-10mg. MDD 30mg. IM haloperidol has greatest risk for EPS side effects. IV haloperidol has greatest QTc-prolonging potential (check if QTc >550).
  - **Diphenhydramine** (PO, IM, IV) 12.5-50mg Sedating, often not used alone but as an adjunct w/ IM Haldol to decrease EPS risk. Used with haloperidol and lorazepam with caution in cases of very severe agitation/physical aggression ("5-2-50")
  - **Hydroxyzine** (PO) 25-50mg antihistamine with anxiolytic effects, rapid onset. Delirium risk.
  - **Risperidone** (PO, ODT) 0.5-2mg. MDD 8mg. NOTE: highest risk of EPS among second generation antipsychotics.
  - **Chlorpromazine** (PO, IM, IV) 25-100mg. Can lead to hypotension (use cautiously in patients with borderline/low blood pressure). Can also lower seizure threshold. Avoid in pregnancy. IM formulation associated w/ sterile abscess formation.
  - **Lorazepam** (PO, IM, IV) 0.5-2mg. Use cautiously in elderly and patients with COPD/OSA due to risk for delirium and respiratory depression, respectively. NOTE: **do not** co-administer parenteral benzos with parenteral olanzapine within 4 hours (risk of lethal respiratory depression).
- Special populations
  - **Geriatric:** PO, consider trazodone 12.5-25mg, quetiapine 12.5-25mg. If cannot take PO, consider olanzapine 2.5-5mg IM/IV
  - **<18 years of age:** If <35kg, can do clonidine 0.05mg PO. If >35kg, can do clonidine 0.1mg PO. If severe and unable to take PO, can do olanzapine (<25kg: 1.25mg olanzapine IM, 25-70kg: olanzapine 2.5mg IM, >70kg: olanzapine 5mg IM).
  - **Parkinson's/Lewy Body Dementia:** quetiapine 12.5-50mg PO, or lorazepam 1-2mg IM or 0.5-1mg IV.

Psychiatry

Delirium

DELIRIUM: definition per DSM-V-TR

1) disturbance of consciousness (i.e. a reduced ability to focus, sustain or shift attention)
2) additional disturbance in cognition (memory, disorientation, language, visuospatial ability, or perception);
2) change from baseline, develops over a short period of time (usually hours to days), tends to fluctuate
4) not better explained by another preexisting neurocognitive disorder and does not occur in the context of a severely reduced arousal/coma

Complications: a/w ↑mortality (JAMA 2010;304:433), ↑institutionalization (Lancet 2014;383:911), ↓cognition (NEJM 2012;367:30)

RECIPE FOR DELIRIUM= VULNERABLE BRAIN + ACUTE INSULT

- Vulnerable brain: older age, history of: stroke, dementia, TBI, vascular disease/ HTN, SUD, visual/hearing impairment, pre-existing psychiatric disease, HIV
- Acute insult: Life-threatening etiologies (**WHHHHIMPS**): **W**ernicke's, Hypoxia, **H**ypoglycemia, **H**ypertensive encephalopathy, **H**yper/hypothermia, **I**ntracerebral hemorrhage, **M**eningitis/encephalitis, **P**oisoning (incl. iatrogenic), **S**tatus epilepticus
    - Other considerations: states of inflammation such as infection (↑ permeability of the blood brain barrier), disturbances or big swings in HR/BP (esp. in pts with vascular disease, ↓ cerebral perfusion, common after surgery), intoxication (including iatrogenic), withdrawal, metabolic disturbance, endocrinopathy, vitamin deficiencies, toxins

DELIRIUM EXAM

- **4AT tool** (available in MDcalc)- Sp/Sn 88% (AAG 2021; 50:733)
- Tests level of consciousness, attention, orientation and acuity

AVOID DELIRIUM BY PREVENTING IT IN VULNERABLE PATIENTS

- **Minimize deliriogenic meds**: anticholinergics, antihistamines, benzodiazepines, opioids
- **Ensure:** no urinary retention, regular bowel movements, and adequate pain management
- **Precautions**: frequent reorientation, mobilize with PT/OT, OOB to chair, **glasses/hearing aids**, minimize lines/telemetry/catheters, early volume repletion if c/f dehydration. **Avoid** room changes or physical restraints (JAMA 2017;318:1161)
- **Anticipate circadian dysfunction**: standing melatonin 3mg **q6PM**, lights on during day and off at night, schedule meds for earlier in evening, avoid late diuresis, reduce noise

DELIRIUM MANAGEMENT

Most important step: identify **UNDERLYING CAUSE** w/ special attention to life-threatening conditions (see Recipe for Delirium, above)**:**

- Maintain IV access if possible
- Behavioral management: implement delirium precautions, modified deliriogenic medications, treat circadian dysfunction
- **Monitor QTc daily** (goal <550ms); daily repletion of K>4 & Mg>2 (in anticipation of pharmacotherapies)
- Reserve pharmacologic agents for **dangerous behavior ONLY** i.e. if **danger to self or others**; no evidence for altering duration of delirium (NEJM 2018;379:2506), severity, hospital or ICU LOS (JAGS 2016;64:705) with increased potential for adverse effects (e.g. QTc prolongation and drug interactions)

Behavioral/environmental management >> 1:1 sitter (re-orients) >> meds >> restraints (deliriogenic)

Medical Management (NEJM 2017; 377:1456)

- **For HYPERactive delirium/AGITATION → start low + PRN, escalate to scheduled** (see *Agitation*)
    - Haloperidol- least sedating, IV>PO as reduces EPS risk 0.25-0.5mg IV q30-60m PRN vs 0.5-1mg PO q4h PRN vs. IM q1h PRN
    - Olanzapine- most sedating, lowest EPS risk - 2.5-5mg SL/PO/IM qd-q4h PRN
    - Quetiapine- PO only, 12.5-25mg PO q1h PRN
- **If continued severe agitation or requiring > 2 doses antipsychotic → consider Psychiatry consult**:
    - Haloperidol PRN: double PRN dose q20 min until effective, ~5-20mg IV
    - Quetiapine PRN: standing 25-50 mg TID, extra dose HS
    - Olanzapine PRN: standing 2.5-10 mg BID, extra dose HS
- QTc ↑severity: haloperidol > quetiapine > olanzapine; Δ tx if QTc ↑ by 25-50%, QTc>500, ⊕U-wave/T-wave flattening
- **Discontinue when able. Prolonged antipsychotic use in elderly can increase mortality**
- **Avoid benzos as may worsen delirium**, though warrants risk/benefit as in some cases risk of withdrawal > risk of continuing
- For patients with prolonged QTc or refractory symptoms to medications, discuss with psychiatry

WHEN TO CONSIDER PSYCHIATRY CONSULTATION

- **Escalating/persistent delirium**, underlying neurodegen, d/o (esp. PD), hx TBI, psych d/o, SUD
- Significant co-morbidities (CV disease/critical illness)
- **Know the following prior to calling:** workup done thus far to identify underlying cause and past/current medication list

WHEN TO CONSIDER NEUROLOGY CONSULTATION

- New focal finding suggesting stroke: *Stroke* Neuro p*20202*
- Other concerning findings (convulsions, meningismus, e/o elevated ICP, abnl spot EEG/LP): *General Neuro p20702*
- **Know the following prior to calling:** last seen well, baseline deficits, anticoagulation

Pooja Menon & Julia Probert

Psychiatry

Psychosis

MENTAL STATUS: document **daily** if new AMS or worsening psychiatric sx (AFP 2009;80:809)

APPEARANCE/BEHAVIOR: grooming/hygiene, eye contact, attitude/cooperation, abnormal mvmt (fidgeting, tics, TD)
SPEECH/LANGUAGE: mechanics: rate, volume, prosody, articulation, and fluency. Watch for speech latency, paucity of speech, mutism, echolalia (copying provider's speech), verbigeration (repeating meaningless phrase like a "broken record")
THOUGHT PROCESS: linear, logical, goal-directed vs. disordered. Types of thought disorder: circumstantial (non-linear; initially veers off but still goal-directed) > tangential (nonlinear, not goal-directed; ultimately loses topic entirely) > flight of ideas (rapid jumps between somewhat-connected thoughts) > word salad (incomprehensible speech). Disorganization: deficiencies in logical organizing of thoughts needed to achieve goal. Thought blocking: interruptions in thought causing inability to respond).
MOOD/AFFECT: Mood: subjective description of emotional state. Affect: physical expression of emotional state
THOUGHT CONTENT/PERCEPTIONS: SI/HI, delusions vs overvalued ideas, hallucinations, obsessions, poverty of content
COGNITION: level of consciousness, orientation, Luria sequence, MOCA
INSIGHT/JUDGMENT: insight: pt recognizes sx as pathological/accepts dx). Judgment (pt's action based on insight)

PSYCHOSIS WORKUP AND DIFFERENTIAL DIAGNOSIS

- **Characteristics**: delusions, thought/behavior disorganization, auditory > visual hallucinations (visual = often neuro/medical, esp. delirium, dementia, alcohol withdrawal)
- **Ddx**:
  - Psychotic/mood disorder: schizophrenia (no clinically significant mood episodes), schizoaffective (primarily psychotic disorder w/ some mood episodes), mood disorder w/ psychotic fx (primarily mood disorder w/ some psychotic symptoms)
  - Neurocognitive disorder: intellectual disability, autism spectrum, dementia and neurodegenerative disorders
  - Medical mimics: **delirium (visual hallucinations)**, migraine, steroid-induced, lupus encephalitis, porphyria, Wilson's, epilepsy, autoimmune/paraneoplastic encephalitis, Charles Bonnet syndrome
  - Substance induced: Can exclude if hx of psychosis during sobriety. GABAergic (i.e. EtOH, benzo) withdrawal (VH, formication; 24hrs - 5d); cocaine/amphetamine intoxication (persecutory delusions, formication); cannabis intox (paranoia, persecutory delusions); hallucinogen intox (VH, paranoia). Note: isolated opioid intoxication/withdrawal does **not** typically include psychosis.
  - New-onset primary psychotic disorder in >50yo is rare. Medical causes (delirium, dementia, CNS pathology) more likely
  - **Refer to psych**: outpatient = always, inpatient = if decompensated ± safety concerns
- **Labs**: CBC, BMP, TSH, CRP, UA, tox screens (should include **separate order for urine cannabinoids** as these are no longer routinely tested for but critical for dx), med levels, delirium w/u (see *Delirium*). Consider RPR, HIV, B12, ANA, pregnancy. Imaging not routinely indicated unless atypical presentation or neuro/medical etiology suspected.

TREATMENT BASICS

- **General principles:**
  - Confirm home antipsychotics/mood stabilizers early in admission & continue *only if* pt reliably taking; otherwise, dose reduce/hold pending psych consult. Ask if pt on long-acting injectable meds/date of last injection and which PRNs work well. Get collateral from DMH case manager, family, shelter, or Freedom Trail Clinic (if on clozapine). Hold if catatonia on ddx.
  - If on >1 standing antipsychotic, confirm before ordering (otherwise avoid). If on valproate, Li, clozapine, check level ASAP.
  - Continue home benztropine, benadryl, propranolol, clonidine (if prescribed) to reduce EPS. Note: lamotrigine has SJS risk, if not taking for >2-3 days re-start at 25mg QD, uptitrate q2w (contact pharmacy/psych for questions).
- **Clozapine**: Uniquely effective, but many SE. Continue inpatient (withdrawal catatonia if stopped suddenly).
  - Neutropenia agranulocytosis in <1% of pts (84% w/in first 3mo); weekly CBC for first 6mo, biweekly for next 6mo, then monthly. May need to DC if ANC <1.5k. **Requires REMS training/monitoring, consult psych/pharmacy w/ questions.**
  - Risk for myocarditis, withdrawal catatonia, constipation/bowel obstruction. Infx can ↓ metabolism and ↑ levels.
  - On admission: continue med to avoid w/d catatonia, ensure bowel reg ordered/effective, check levels if infection or smoker
- **Extrapyramidal symptoms (EPS)**:
  - Dystonia: muscle spasm incl. oculogyric crisis (**risk of rapid airway obstruction**), torticollis, trismus, opisthotonos, laryngospasm. **Tx**: anticholinergics (benztropine, diphenhydramine)
  - Pseudoparkinsonism: reversible; bradykinesia, tremor, rigidity, masked facies, shuffling gait. **Tx**: anticholinergics
  - Akathisia: subjective feeling of inner restlessness, inability to stay still. **Tx**: low dose BB (e.g. propranolol)
  - Tardive dyskinesia (TD): Involuntary, repetitive, arrhythmic movements: lip smacking, chewing, puckering, writhing. Occurs w/ long-term antipsychotic use, often irreversible. May use VMAT2 inhibitors to treat.

ANTIPSYCHOTICS & SIDE EFFECTS (AFP 2010;81:617)

	Anti-cholinergic	Prolong QTc	EPS	NMS	Prolactin ↑	Postural hypoTN	Sedation	HLD	Wt gain	DM2	Sexual dysfxn
haloperidol	+	+	++	++	+++	+	+	+	+	+	++
chlorpromazine	+++	++	+	+	++	+++	+++	++	++	+	+++
aripiprazole	0	+	+	+	0	+	+	0	0	+	+
olanzapine	+	+	+	+	+	+	++	+++	+++	++	+
quetiapine	+	+	0	+	0	++	++	++	++	+	+
risperidone	0	+	++	+	+++	++	+	+	++	+	++
ziprasidone	0	++	+	+	+	+	+	0	0	+	+
clozapine	+++	+	0	+	0	+++	+++	+++	+++	++	+

Psychiatry Catatonia, NMS, & Serotonin Syndrome

CATATONIA

- *Behavioral syndrome* due to underlying condition that can occur in the context of many psychiatric, neuro, or medical dx; marked by inability to move or communicate despite full physical capacity; waxes/wanes; pathophysiology incompletely understood
- **Subtypes**: stuporous: immobility, mutism, withdrawal; excited: hyperkinesis, stereotypy, disorientation; malignant (medical emergency): sx accompanied by hyperthermia, autonomic instability, rigidity (Arch Gen Psych 2009;66:1173)

Etiology: (Schizophr Bull 2010;36:239; Behav Brain Sci 2002;25:555)

- Psychiatric: mood disorders (e.g. bipolar d/o) > thought disorders (e.g. schizophrenia, autism) > dissociative disorders
- Neuro/medical: seizures/NCSE, PRES, CNS lesion, infection, TBI, delirium, anti-NMDAR encephalitis, PLE, SLE
- Drug: dopamine-blockers, dopamine withdrawal, sedative/hypnotic withdrawal, hallucinogens, synthetic MJ, opiates

Diagnosis: (Psych Scand 1996;93:129.; DSM-5 TR 2022;6:135; Arch Gen Psych 2009;66:1173):

- Bush-Francis Catatonia Rating Scale (BFCRS)– 14-item screening (positive when ≥ 2 items) and 23-item rating scales (Positive when ≥ 4 items) OR the presence of 2-4 of the below signs for several hours:

Observed Signs	Elicited Signs
-Immobility: Hypo-akinetic, not influenced by external stimuli -Stupor: Decreased alertness, diminished response to voice/painful stimuli -Excitement: Impulsive, stereotypic behavior -Mutism: Verbally unresponsive while awake -Speech mannerisms: Robotic speech, foreign accent, palilalia -Behavioral mannerism: Odd, purposeful movements -Posturing: Voluntarily maintaining a posture for a long time -Echophenomena: Echolalia/echopraxia (mimic sound/movement) -Stereotypy: Awkward non-goal-directed repetitive movements. -Staring: Fixed gaze	-Ambitendency: Stuck on hesitant movement when the examiner verbally contradicts own nonverbal signal (extend hand and say "do not shake my hand") -Waxy flexibility: rigid tone that is gradually overcome -Automatic obedience: "Stick out your tongue. I want to write on it with a pen." (pt will stick out tongue) -Negativism: Opposite/no response to instruction. -Stimulus-bound behavior: Behavior tied to certain stimuli

- Lab findings: Leukocytosis (15,000 - 25,000), CK ≥ 1000, and ↓ serum iron in malignant catatonia.
- Lorazepam Challenge: **2mg IV x1** (0.5-1mg in frail/elderly). Partial relief of signs after 5 -10 minutes after is consistent with a diagnosis of catatonia (Arch Gen Psych 2009;66:1173). Negative challenge test does NOT rule out catatonia.
- **Differential dx**: delirium, dementia, stroke, PD, stiff person & locked-in syndromes, NCSE, akinetic & elective mutism, anti-NMDAR encephalitis; If **malignant***:* NMS, malignant hyperthermia, SS, DT, CNS infection/vasculitis, anticholinergic toxicity

Treatment: (Gen HospPsychiatry 2017;48-1)

- **Always consult psych. NO antipsychotics/other D2 blocking meds.** Trend CK, BMP; q4h VS; supportive care.
- Treatment: 2mg IV lorazepam q6-8h, uptitrate as tolerated. Hold for respiratory depression only, NOT sedation (catatonia sx can mimic sedation). If no response → **ECT, amantadine/memantine, anticonvulsants**

NEUROLEPTIC MALIGNANT SYNDROME (NMS) (Am J Psych 2007;164:870)

- **Overview**: abrupt onset of 1) Δ in mental status 2) rigidity 3) fever 4) autonomic dysfunction (tachy, HTN, diaphoresis), associated with medication change that causes decreased dopaminergic tone (med list: Neurohospitalist 2011;1:41)
- **Risk factors**: initiation/increase of dopamine-blocking med or withdrawal of pro-dopamine med (typically occurs within hours/days, but can be idiosyncratic), withdrawal from EtOH/sedatives, hx of NMS/catatonia, basal ganglia d/o, exhaustion, dehydration, agitation
- **Labs**: ↑WBC and CK>1000 (correlates w/severity) most common, ↓ serum iron, mild ↑ LDH/alk phos/AST/ALT, ↑↓ electrolytes
- **Ddx**: serotonin syndrome, malignant hyperthermia, malignant catatonia (significant overlap), CNS infection, spinal cord injury, seizure, heat stroke, acute dystonia, CNS vasculitis, thyrotoxicosis, drug intoxication/toxicity, withdrawal states

Stage	Clinical Presentation	Intervention/Treatment
Early	Mild rigidity, confusion, T<100.4F, HR <100	• Stop offending agent & contributors (serotonergics, Li, anticholinergics) • Aggressive fluids/supportive care ± **lorazepam** 0.5-2mg IV q4-6h
Moderate (may require ECT)	Moderate rigidity, T100.4-104F, HR 100-120	• Cooling measures ± ICU • **Bromocriptine** 2.5mg PO q8h *or* **amantadine** 100mg PO q12h
Severe (may require ECT)	Severe rigidity, ± coma, T >104F, HR >120	• ICU level of care (if intubation required, midaz > propofol for sedation) • **Dantrolene** 1-2.5mg/kg IV q6h x48h

SEROTONIN SYNDROME (SS) (NEJM 2005;352:1112)

- **Overview**: Exposure to serotonergic agent(s) leading to 1) Δ mental status 2) neuromuscular hyperreactivity (tremor, clonus, hyperreflexia) 3) autonomic instability (tachycardia, tachypnea, diaphoresis, mydriasis, hyperthermia, shivering, sialorrhea, hyperactive bowel sounds, diarrhea). Watch for rhabdo/AKI. *Note:* n/v/d common in SS prodrome but rarely seen in NMS
- **Causative agents**: amphetamines, bupropion, buspirone, carbamazepine, carbidopa-levodopa, cocaine, cyclobenzaprine, diphenhydramine, ergotamines, fentanyl, linezolid, lithium, LSD, MAOIs, MDMA, meperidine, methadone, methylene blue, metoclopramide, mirtazapine, ondansetron, SNRIs, SSRIs, St. John's wort, TCAs, tramadol, trazodone, triptans, tryptophan, VPA
- **Diagnosis**: Hunter's Criteria 84% sensitive 97% specific (QJM 2003;96:635)
- **Treatment**: 1) hold offending agent (generally will resolve within 24h), 2) use BZDs if agitation present (**lorazepam** 1-2mg IV, repeat PRN to effect), 3) if unsuccessful, can use **cyproheptadine** 12mg x1 then 2mg q2h until clinical response seen. Very severe cases with hyperthermia may require ICU level of care with cooling, intubation, sedation, and paralysis.

MAJOR DEPRESSIVE DISORDER (MDD)

- Epidemiology: common in general population. U.S. lifetime prevalence ~20%, F>M (JAMA Psych 2018;75:336)
- Screening: USPSTF recommends **universal screening of adult primary care patients including pregnant and postpartum women** (Grade B): Use **PHQ-2**: to begin screening (AFP 2012;85:139); **PHQ-9** to complete screening (AFP 2012;85:139)
- DSM-5-TR criteria: (mnemonic SIGECAPS): must have depressed mood and/or loss of **I**nterest/pleasure + ≥4 of following sx: change in **S**leep, worthlessness/**G**uilt, fatigue/decreased **E**nergy, poor **C**oncentration, change in weight/**A**ppetite, **P**sychomotor agitation/slowing, thoughts of death (not just fear of death) or **SI**.
  - Sx must be present over same **2w period** & cause significant **impairment/distress**
  - Ddx: other psych (e.g. bipolar, adjustment disorder, persistent depressive disorder, primary thought disorder, borderline personality disorder, prolonged grief), drugs/meds, OSA, hypothyroidism, stroke, TBI, delirium, vit def, dementia, MS, HIV
- Tx: psychotherapy ± medication as determined through shared decision making; combination > either alone (pharmacology > therapy) (APA 2019; J Clin Psychiatry 2008;69(11):1675-85)
  - SSRIs are 1st line: All second-generation antidepressants are roughly equivalent (consider starting with **sertraline or escitalopram** as they have best combination of efficacy and acceptability (Lancet 2009;373:746)).
  - Response time for SSRIs may vary between 1-2 weeks up until 8-12 weeks, with an average of 6-7 weeks (Am J Psychiatry 2006 163(1):28-40)
  - Other common options: bupropion, mirtazapine, & SNRIs. Bupropion lowers seizure threshold and is contraindicated in pts with risk of seizure (seizure disorder, eating disorder, etc.), may aid in smoking cessation; caution in pts with renal/hepatic impairment (↑ concentration) or with cardiovascular disease (↑ BP). SNRIs may also ↑ BP.
  - Consider mirtazapine in elderly pts with frailty (sedative and ↑ appetite).
  - Use Mayo Clinic Depression Medication Decision Aid to choose meds based on side effect profile
  - Risk of death in TCA overdose, advising caution when Rxing TCAs to patients with history of suicidality or serious attempts
  - Other common uses of antidepressants:
    - Anxiety disorders: SSRIs, SNRIs
    - Neuropathic pain: SNRIs, TCAs
    - Insomnia: trazodone, mirtazapine
    - Functional GI disorders: amitriptyline for IBS-D & dyspepsia, nortriptyline/fluoxetine for constipation (WJG 2009;15:1548-53)
- **Pregnant pts.** In mild/moderate MDD, consider psychotherapy as first line tx. In severe, or if psychotherapy is not available/preferred, consider medication. If prior successful tx trial, consider using that same antidepressant,

Side Effect Profiles of Commonly Prescribed Antidepressants (Can J Psychiatry 2016;61:540; NEJM 2005;353:1819)

Class	Drug	Anti-Cholinergic	Drowsiness	Insomnia/ Activation	Nausea/ Vomiting/Diarrhea	Wt Gain	SexualDysfn	Orthostatic HoTN	↑ QTc	Usual Daily Dose (mg)
SSRI	Citalopram	-	-	+	+	+	+++	+	++	10-40
	Escitalopram	-	-	+	+	+	+++	+	+	5-20
	Fluoxetine	-	-	++	+	+	+++	+	+	20-80
	Paroxetine	+	+	+	+	++	++++	++	-	20-50
	Sertraline	-	-	++	++	+	+++	+	+	50-200
SNRI	Duloxetine	-	-	+	++	-	+	-	-	30-60
	Venlafaxine	-	+	+	++	-	+++	-	+	37.5-225
Atypical	Bupropion	-	-	++	+	-	-	-	+	150-450
	Mirtazapine	+	++++	-	-	++++	+	-	+	15-45*
SerotoninModulator	Trazodone	-	++++	-	++	-	$	++	++	100-400*
	Vilazodone	-	-	++	+++	-	+	-	-	10-40
	Vortioxetine	-	-	+	+	+	+	-	-	10-20
TCA	Amitriptyline	++++	++++	-	+	++++	++++	+++	+	25-300*
	Nortriptyline	++	++	-	-	+	+++	+	+	25-150*

$ Risk of priapism

Dosing of Antidepressants

- Start at low dose, titrate q1-2 weeks. Adequate trial is 6-12 weeks at full dose; if poor tolerance/response after 4-6 weeks, augment with psychotherapy or other medications; consider switching SSRIs
- Advise pts of initial side effects that they will develop tolerance to (GI upset, headache, sedation/activation, dizziness). Advise pts that physical sx of depression (sleep disturbance, appetite changes) usually resolve first, within days-weeks. Mood sx may take weeks to resolve. Sexual side effects (ED, anorgasmia, delayed ejaculation) may persist.
- Continue antidepressants for at least 6 months after symptom remission to prevent relapse
- Stopping any antidepressant requires tapering off over 2-4 wks to prevent discontinuation syndrome (affective sx, flu-like sx, sleep disturbance, GI upset, dizziness/balance/sensory sx, electrical sensation or 'brain zaps'). MAOIs reduction may cause psychosis.
  - Paroxetine (short half-life, most likely to cause discontinuation sx): taper down 5-10 mg weekly over 4+ weeks
  - Fluoxetine (long half-life): taper may not be needed for doses < 40 mg daily; if ≥ 40 mg daily, taper over 2 wks
  - If pt develops discontinuation sx, restart antidepressant or increase dose, then taper more gradually over 6-12 weeks

When to Refer to Psychiatry: concern for bipolar disorder (any history of mania/hypomania), failure of ≥2 adequate rx trials, severe MDD with SI/HI, psychosis, or catatonia.

Generalized Anxiety Disorder (GAD)

- Epi: US lifetime prevalence 8%, 2-3x more prevalent among F vs M. (AFP 2022;106:157).90% will meet criteria for at least 1 co-morbid psych condition in their lifetime (MDD, dysthymia, AUD, simple phobia, social anxiety) (Arch Gen Psych 1994;51:355)
- Excessive worry associated w/ poor CV health, ↑CAD, ↑CV mortality (Nat Rev 2012;9:360)
- Screening: USPSTF recommends screening of adult primary care patients (Grade B). GAD-7: score ≥5 indicates mild GAD (97% Sn, 57% Sp, LR 2.2); score ≥10 indicates moderate GAD (89% Sn, 82% Sp, LR 5.1) (Arch Intern Med 2006;166:1092).
- DSM-5-TR criteria:
  - A) excessive anxiety/worry occurring most days for ≥6mo re: multiple life domains, that is
  - B) difficult to control, and
  - C) associated w/ ≥3 sx: restlessness, fatigue, poor concentration, irritability, muscle tension, sleep disturbance. Must also cause
  - D) significant distress/impairment; and
  - E/F) not better explained by drugs/meds/other psych disorders
- Tx: 1st line therapy = **SSRIs/SNRIs** and/or CBT, based on availability/pt preference; no head-to-head trials (meta-analyses have found effect sizes ≈ equivalent). No individual SSRI/SNRI shown more effective; SSRIs have lower risk of insomnia/activation over SNRIs. **Escitalopram, citalopram, and sertraline** generally preferred due to fewer side effects.
  - Advise pts that symptoms may take 4-6 weeks to resolve. For first few days, anxiety and activation may worsen as SSRI takes effect. See *Depression* for dosing guidelines.
- Adjunctive therapy: Consider buspirone 10 mg, increase by 10mg/day q1-2weeks (note: little efficacy as an acute anxiolytic); gabapentin 300- 800 mg TID; hydroxyzine 25-50 mg QID; lorazepam or clonazepam 0.5-1 mg PO BID PRN for 4-6 wks while SSRI takes effect. If refractory, psychiatry may start risperidone/quetiapine. Counsel pt on dependence of BZD, and consider non-BZD options first if history of substance use.

Refer to Psych: need for CBT, failure of 2 adequate SSRI/SNRI trials, severe GAD w/ recurrent panic, SI

Panic Disorder

- Epi: US lifetime prevalence ♀7.0% & ♂3.3% (AFP 2015;91:617)
- DSM-5-TR criteria: A) Recurrent unexpected panic attacks; B) >1 month of persistent worry about panic attacks or their consequences, or >1 month of significant maladaptive change in behavior related to attacks; C/D) sx not better explained by drugs/meds/other psych disorders (e.g. social anxiety disorder, specific phobia, OCD, PTSD)
- Workup for panic attacks: vitals, ECG, BMP, CBC, thyroid panel, HCG, tox screen. Consider testing for pheochromocytoma, seizures, OSA, asthma/COPD if any clinical suspicion
- Treatment: 1st line = CBT and/or SSRI (equally effective). See GAD above for adjunctive therapies during SSRI initiation

Refer to Psych: need for CBT, severe symptoms, failure of 2 SSRI trials, SI

Post-Traumatic Stress Disorder (PTSD)

- Epi: US lifetime prevalence 6%: ♂4.1%, ♀8%; higher in combat/severe disaster survivors (AFP 2023;107:273)
- Screening: Primary Care PTSD Screen (PC-PTSD-5): screens for trauma exposure then for sxs based on DSM criteria; score >4 with Sn 100%, Sp 85.2% (J. Clin. Psychol 2022;78:2299), though cutoff of 3 may be more accurate for female pts due to higher false negative rates (JAMANTW 2021;4)
- DSM-5-TR criteria:
  - A) exposure to trauma
  - B) intrusive sx (recurrent, involuntary trauma memories/dreams, dissociative flashbacks, psych distress, marked physiological reactions to trauma reminders)
  - C) avoidance sx (of trauma reminders)
  - D) neg cognition & mood (incl amnesia of trauma, neg beliefs about self/others/world, inappropriate self-blame, neg emotional state)
  - E) hyperarousal (irritability/anger, reckless/self-destructive behavior, hypervigilance, exaggerated startle, sleep disturbance); lasting **>1mo** & causing significant distress
- Treatment: trauma-focused therapy + SSRIs/SNRIs; tx of psych/SUDs comorbidities; clonidine, atypical antipsychotics; prazosin 1mg nightly, increasing 3-15mg over few months for sleep disturbance. Counsel pt on risks of orthostasis and rebound HTN for prazosin/clonidine if discontinued abruptly. **All care/conversations should be trauma-informed, recognizing that not all patients are ready to discuss trauma (and avoid probing patients on their trauma if so).**

Refer to Psych: all should be referred for psychotherapy ± pharmacotherapy (depending on complexity of needs)

Obsessive-Compulsive Disorder (OCD)

- Epi: US lifetime prevalence 2.3%. Mean age of onset ~19-20, rarely develops after early 30s (AFP 2015;92:896)
- DSM-5-TR criteria: A) presence of obsessions (recurrent and persistent thoughts/urges/images that are intrusive and unwanted, and that pt tries to suppress) and/or compulsions (excessive or unconnected repetitive behaviors/mental acts that pt feels compelled to perform in response to obsessions or rigid rules to reduce or prevent anxiety/distress); B) obsessions/compulsions are time-consuming or cause significant distress/impairment; C/D) sx not better explained by drugs/meds/other psych disorders
- Treatment: 1st line = ERP and/or SSRI depending on pt preference, severity of OCD, and presence of depressive sx. Combination tx is most effective (Curr Neuropharmacol 2019;17:710). Adequate trial of SSRI is maximum tolerated dose for 12 weeks. OCD pts typically require higher doses than for other indications. If good response to SSRI, duration of treatment should be *at least 1-2 years* with taper off over several months (AFP 2015;92:896). 2nd line = clomipramine, venlafaxine, or atypical antipsychotics

Refer to Psych: need for CBT, severe symptoms, failure to respond to 2 high-dose SSRI trials, SI

Psychiatry

Alcohol Use Disorder & Withdrawal

Substance Use - General Principles

Screening: Ask all primary care pts & inpatients about current and lifetime substance use. USPSTF recs screening for *unhealthy* use.

- EtOH: AUDIT-C screens for unhealthy use, CAGE detects dependence
- Other substances: "How many times in the past year have you used a recreational drug or used a prescription medication for nonmedical reasons?" (Arch Int Med 2010)

History

- Most recent use, quantity, frequency, route of ingestion, triggers for use
- Benefits vs. harms of use; medical, psychiatric, and behavioral complications of use; harm reduction practices
- Age of first use, family hx of use disorders, periods of abstinence
- Treatment hx: Medications, structured treatment settings, mutual support groups. Current goals (↓ amt or freq of use vs. abstain) *"What would you like to see next for yourself?"*

Diagnosis

- **Use ≠ disorder.** Assess for use disorder of all substances reported by number of DSM-5-TR criteria met (impaired control, social impairment, risky use, and pharmacological criteria): 2-3 = mild, 4-6 = moderate, ≥6 = severe. Once criteria for use disorder is no longer met, can classify as early remission (<1y) or sustained remission (>1y).
- Ask about 1° vs. 2° substances used. *"Of the substances you use, is there one you identify as the biggest problem?"*
- Avoid using Polysubstance use disorder ≠ DSM diagnosis = stigmatizing while being diagnostically/therapeutically meaningless.
- Tox screens alone should not be used to diagnose SUDs. False positives and negatives are possible. It is not recommended to alter prescribing patterns for meds based on tox screens. Use tox to check for concomitant substance use, monitor opioid use, and initiate conversations around use with patients.

DSM-5-TR Criteria for SUDs

1. Substance taken in **larger amounts** and/or over a longer period than intended
2. **Unsuccessful efforts to cut down** or control use
3. A **great deal of time is spent** to acquire, use the substance, or recover from effects
4. **Craving** or strong desire or urge to use the substance
5. Recurrent use resulting in a **failure to fulfill major role obligations** at work, school, or home
6. Continued use despite **persistent/recurrent social or interpersonal problems**
7. Important social, occupational or recreational **activities given up** or reduced because of use
8. Recurrent use in **physically hazardous situations**
9. Use continued despite persistent or recurrent **physical or psychological problem** that is likely caused or exacerbated by the substance
10. **Tolerance**, defined as ↑amount of substance to achieve desired effect; or ↓ effect w/ same amount
11. **Withdrawal**, defined as characteristic withdrawal syndrome for the substance; or pt is taking substance to relieve or avoid w/d sx

Approach: Person-first language and trauma-informed care. People w/ SUD experience bias and discrimination from healthcare providers. Address drivers of self-directed d/c: pain, agitation, discomfort, treating w/d, and allowing pts to leave the floor (MGH policy) (Subst Abus 2020;41:519). Involve ACT ("Substance use team") early. Consider risks of escalation before directly involving security (ex: may have security in hall on standby).

Treatment: Medications: many can be prescribed by PCP, except for methadone. Counseling: MI, CBT; Peer support: recovery coach, mutual help meetings (AA/SMART recovery). See Boston Area and MGH SUD Resources.

SUD Levels of Care

Levels of care usually progress from hospitalization/"detox" " CSS " TSS " long-term residential tx " sober living

Inpatient			Outpatient		
Acute Treatment Services (ATS): Medically Supervised Withdrawal/ "Detox"	Clinical Stabilization Service (CSS)/Transitional Support Service (TSS)	Dual Diagnosis Units	Long-Term Residential Treatment ("Halfway Houses")	Partial Hospitalization Program (PHP)	Intensive Outpatient Program (IOP)
-Medical mgmt of acute w/d in a standalone detox center. -Not best for pts with risk of severe alcohol withdrawal. -LOS: 4-7d -Patients cannot go to ATS once admitted to the hospital	-Inpt programs to transition from ATS/hospital to longer treatment; very structured with counseling. -Usually go from CSS to TSS. -D/c coord: ACT SW -LOS: 14d (CSS), 30d (TSS)	-Inpt locked psych unit, address comorbid SUD + 1° psych disorders. -Often reserved for pts w/ severe comorbid sx +/- acute safety concern. (i.e mania, psychosis, SI) -D/c coord: Psych c/s -LOS: 3-5d	-Covered by insurance -Offer groups, counseling and attendance at outside mutual support -Few offer meds esp in OUD (JAMA 2020;324:804). -D/c coord: ACT SW -LOS: 6-12mo	-Highly structured outpt treatment, 6-8h/d for 5d/w. -Intensive group therapy; tx for both SUD and MH concerns. -D/c coord: Psych -LOS: 1-3w	-Outpt., less intensive than PHP; usually ~3h/d for 3d/w -Provides psychoeduc./therapy. -D/c coord: ACT SW -LOS: 1-3mo

Alcohol Use Disorder (AUD)

Diagnosis and Health Effects

- Diagnose AUD w/ DSM criteria. Quantify use to counsel re: risks. 1 standard drink = 14g ethanol (5oz wine, 12 oz beer, 1.5 oz spirits)
- Risky use ↑ risk for health consequences (not part of SUD criteria). Includes drinking while pregnant; binge drinking: ≥5 drinks/occasion for men, ≥4 for women; heavy drinking: ≥15 drinks/wk for men & ≥8 drinks/wk for women or binge drinking 5 or more days the past month (NIAAA).
- Chronic use: Cytopenia (low Hb, WBC, Plt); low K/Mg/Ca/Phos/VitD (EtOH toxic to renal tubules and ↓GI absorp); ketoacidosis (↓ gluconeogenesis → rel. hypoglycemia → ↓ insulin → ketosis); lactic acidosis (↑ratio of NADH/NAD) (NEJM 2017;377:1368)

Treatments for Moderate-Severe AUD

- Psychosocial: See above. 12-step progs ↑ rate of continuous abstinence compared to other counseling methods (Cochrane Rev 2020)
- FDA approved *first line*: naltrexone, acamprosate; *second line*: disulfiram; data suggests disulfiram efficacy only if dosing is observed (JAMA 2018; 320: 815)
  - Naltrexone (↓reward/cravings) PO 25mg X2d →50mg daily or IM (Vivitrol) 380mg q4w (CI: acute hepatitis/ALF, current opioid use or on bup or methadone). Naltrexone likely > acamprosate (JAMA 2006;295:2003)
    - Assess for OUD first as Naltrexone will block effects of opioids and precipitate withdrawal
  - Acamprosate (↓cravings) 666mg TID (Adjust dose at CrCl <50, CI: CrCl<30, pregnancy)
  - Disulfiram (→ disulfiram-ethanol reaction: nausea, flushing, vomiting, sweating, hypotension, palpitations, rarely serious CV rxs): Start PO 125-250mg daily → 250-500mg/d maintenance dose
    - Only for patients in sobriety wishing to abstain. NOT advised to "reduce" active drinking (JAMA 2018; 320: 815)
- Non-FDA approved: topiramate (100-150mg BID), gabapentin (~600mg TID) (Addiction 2019;114:1547), baclofen (5mg TID -> 15mg TID) (Am J Psych 2018;175:86)
- Success can range from reducing heavy drinking days to abstinence (Addiction 2021;116:1973). Utilize principles of harm reduction. Set goal with patient and use benchmarks to assess treatment efficacy.
- Risk of **malnutrition** with continued alcohol use. Assess lytes. Consider prescribing MVI w/ folic acid, thiamine 100 mg daily (Drug Alcohol Depen 2017;179:229)

Wernicke-Korsakoff Syndrome

- Wernicke encephalopathy (acute):
  - Dx: Caine Criteria (85% Sn) requires ≥2: (1) dietary deficiency, (2) oculomotor dysfxn, (3) cerebellar dysfxn (LE ataxia), (4) AMS or poor memory. Note: Serum B1 NOT diagnostic (J Neuro Nsgy Psych 1997;62:51)
  - Tx: Thiamine IV>IM 500mg (*infuse over 30 mins to prevent anaphylaxis*) TID X7d → 100mg qd until no longer at risk (*not per the Alcohol Withdrawal Orderset. No consensus on dosing or duration of Thiamine. However, adverse effects of excessive Thiamine are uncommon while untreated W-E → irreversible W-K) (Intern Med J 2014;44:911)
  - Ppx in those at risk: IV 200mg X1d > 200mg PO BID X4d (find under Alcohol Withdrawal Orderset – Adjunctive Mediciations) 100mg qd at discharge until no longer at risk
- Korsakoff's (chronic): Antero+retrograde memory deficits (confabulation), apathy, intact sensorium

ALCOHOL WITHDRAWAL SYNDROME

Pathophysiology: GABA (inhibitory) and glutamate (excitatory) work in balance

- Chronic EtOH use: ↑GABA stimulation → glutamate upregulation. After chronic stim, GABA receptors are less sensitive & require more EtOH to balance increased glutamate. Abrupt cessation of EtOH: ↓GABA → unbalanced excess glutamate activity → noradrenergic surge → ↑dopamine release → complicated withdrawal sxs.
- EtOH eliminated via approx 0th-order kinetics: approx. 15-20 mg/dL/hour. Blood EtOH clearance calculator.
- BAC effects vary widely by person and chronicity of EtOH use. For many, BAC can be approximated grossly as: <80 mg/dL: legal driving limit // 100 mg/dL: impaired judgment // 200 mg/dL: confusion/staggering // 300 mg/dL: stupor // 400 mg/dL: coma/death

Evaluation:

- H&P: Time of last drink, hx severe withdrawal & complications (withdrawal seizures, delirium tremens, alcoholic hallucinosis, ICU/intubation), hx of patient-initiated discharge, co-ingestions (including BZD), EtOH use hx and tx, including recent changes in use pattern, assess for active SI and concurrent mental health conditions
- Labs: CMP, CBC, serum osm if HCO3 <15 or AGMA (2/2 ketoacidosis), LFTs, CPK if found down (>5K = rhabdo), tox screen, serum EtOH (clear ~15-35 mg/dL/h, chronic = faster metab, higher tolerance) (J Forensic Sci 1993;38:104), pregnancy test if of childbearing potential > consult OB if in third trimester/at risk of pre-term delivery/concern for Fetal Alcohol Syndrome. Consider testing HIV, HCV, TB if clinically appropriate.

Subtypes and Management: Sx vary by time after last drink, developing within hrs to days after cessation/reduction in use that has been heavy and prolonged (Diaphoresis, HR>100, hand tremor, insomnia, nausea/vomiting, transient visual/tactile/auditory hallucinations, agitation, anxiety, GTCs).

- Prediction of Alcohol Withdrawal Severity Scale: PAWSS
- Initial Tx for all EtOH withdrawal: IV/IM thiamine (See Wernicke-Korsakoff above), D5-LR to fix ketoacidosis, replete lytes (esp Phos/K), folate 1mg qd, MVI, place on CIWA (q1-4h assessment, d/c once CIWA-Ar<8 for 24h), offer ACT ("Substance use team") c/s for AUD treatment
- **Mild withdrawal** (CIWA-Ar <10): Can be managed in ambulatory setting with supportive care (non-ceffeinated fluids, MVI, thiamine 100mg PO 3-5D, RTC precautions) (ASAM 2020); or can consider taper of gabapentin>> PO BZD (Alcohol Clin Exp Res 2009:33:9):
  - Gabapentin 1200mg loading dose + 600mg q6h Day 1 or 1200mg/d 1-3D, tapered to 300-600mg/d up to 4-7D (ASAM 2020)
- **Mild-moderate withdrawal** (CIWA-Ar: 10-18): Within 48h; tremors, sweats, ↑HR, ↑BP, HA, anxiety, intact orientation.
  - **Treat with Rx. Use EtOH withdrawal order set.** Typically BZD >> phenobarbital (unless contraindication to BZD or hx of comp. withdrawal). Some patients benefit from addition of adjunct medication. Consider carbamazepine or gabapentin in addition to BZD.
- **Severe withdrawal** (CIWA-Ar >19): **ALWAYS TREAT, can be fatal. IV** BZD vs. phenobarb using EtOH withdrawal order set, as detailed below. Predictors: hx of DT/sz, comorbidities (especially TBI), age>65, ↑BP, ↓Na/↓K, Plt <150 (JAMA 2018;320:825).
  - **Seizures**: 6-48h; typically 1x GTC or burst of multiple GTCs in a short period. If status epi, consider other etiologies. Should be immediately treated to prevent another seizure. Fast-acting BZD: lorazepam, diazepam
  - **Alcoholic hallucinosis**: 12h-48h; visual/tactile >> auditory (pt typically aware that hallucinations are not real), clear sensorium.
  - **Delirium Tremens (DT)**: 72h-3d, up to 2w; tremors, sweats, ↑HR, ↑BP, fever, disorientation, inattention, hallucinations (pt typically unaware that hallucinations are not real), agitation; usually CIWA >20.

ALCOHOL WITHDRAWAL TREATMENT PROTOCOLS: *Use Epic Alcohol Withdrawal Order Set!*		
	Benzodiazepine (BZD)	**Phenobarbital** (PB)
When to use	Generally 1st line. Mild-mod w/d sx, no recent (within last 2-3 years) complicated w/d	Recent (within last 2-3 years) DTs, seizures, ICU admissions for w/d; patient preference for phenobarb; Resistant Alcohol Withdrawal (RAW)/ Refractory Alcohol Withdrawal: severe or complicated withdrawal or CIWA scores not improving despite high doses of BZD
Notes	CI: Acute angle closure glaucoma Resistance (>6mg lorazepam/h) or BZD toxicity (similar to DTs) w/ escalating dose. Consider switch to phenobarb if CIWA scores not improving despite high doses of BZD	CI: hx SJS/TEN; hx AIP; unstable respiratory status Relative CI: high likelihood of self-dir d/c interrupting therapy, limited period of recent use (ex: completed withdrawal treatment in last 10 days) Side effects: apnea, hypoventilation, ↓HR, ↓BP, laryngeal spasm Medication interactions: CYP3A4 inducer – decreases conc. of many rx including apixaban. May enhance effects of anti-HTN meds.
Mech.	GABA-ergic. $t_{1/2}$ varies by BZD	GABA-ergic and anti-glutamate receptor. Auto-taper, long half-life (1-4d), predictable effect, wide therapeutic window.
Dose	**PO > IV** if able to take PO No evidence showing superiority of effectiveness among BZDs Diazepam, chlordiazepoxide: Longer half life, often preferred for smoother withdrawal course and breakthrough control Lorazepam: (↑half-life, lower risk of oversedation if concerned for liver dx) **PRN**: Use CIWA-Ar scale when patient can appropriately communicate. Avoid treating for subjective symptoms only. Consultants may rec "objective CIWA" if concerned for BZD-seeking **Standing**: If CIWA >19, likely to have severe w/d > consult ACT for consideration/implementation	**Loading dose:** 10mg/kg as 3 divided doses (if worried about oversedation i.e. older age, other sedating meds, high risk of respiratory compromise). No taper in most cases. -**↓dose** (6-8 mg/kg) if **sedation carries high risk**: age>65, TBI, concurrent sedatives, lung dz, decompensated cirrhosis, Received 8-30mg Ativan (or BZD equivalent): **Rescue dose:** 2mg/kg for tremor/tongue fasciculations AND one of the following: SBP>165, HR>115, diaphoresis. DO NOT give for agitation, hallucinations
D/C	Monitor CIWA score, what sx they are scoring for, and total daily BZD requirements. Consult ACT team for assistance w/ pharamacologic and psychosocial mgmt of AUD, or if considering standing BZD taper and unsure of dosing sched.	Assess frequently: IM loading dose is split to allow monitoring: 40% 0h, 30% 3h, 30% 6h. If uncontrolled sx or sedation, call pharmacist. Rescue dose as above. Discharge: phenobarbital increases sensitivity to BZDs/EtOH; **drinking after IV/IM load can be fatal**.

- Clonidine can be used as adjunct for autonomic hyperactivity and anxiety when not controlled by BZD alone.
- Beta-blockers can be used as adjunct in select patients for persistent hypertension or tachycardia. Should not be used alone in tx of alcohol w/d

Psychiatry — Opioid Use Disorder & Withdrawal

OPIOID USE DISORDER (OUD)

- Chronic, relapsing disorder of opioid use due to dysfunction of brain reward circuits (J Addict Med 2015;9:358)
- **Screen** all patients. Confirm diagnosis using DSM-5-TR Criteria for opioid use disorder. Use ≠ SUD. See *SUD General Principles.*
- Focus on building a **therapeutic alliance** and performing risk assessment (Med Clin N Am 2018;102:587)
  - Assess **risk of withdrawal**: current opioids, frequency of use, last use PTA, g/day or $ spent/day, recent withdrawal
  - Assess **treatment readiness**: treatment hx (medications, counseling, mutual-aid organizations), social circumstances (housing, food security, legal issues). Understand patient's current goals, including safer use vs abstinence
  - Assess for **high-risk injection practices**: history of bacterial/fungal complications (endocarditis, SSTIs, bone/joint infections), viral complications (HIV, HCV, HBV). If currently injecting, use PCOI harm reduction conversation guide to review injection practices. Consider **PrEP** for patients with high-risk injection practices (*see HIV/AIDS*)
  - Assess **risk of overdose**: h/o OD, h/o psychiatric (i.e. mood) disorder or suicidality, ↓tolerance from recent incarceration or abstinence-based treatment, access to naloxone, high-dose Rx'd opioids and/or other sedatives (check PDMP), incr alcohol use, injection use, respiratory disease, severe chronic pain (Addiction 2015;110:996; Lancet 2019; 393: 1765)
- Labs: serum/urine tox (fentanyl now included in urine tox but may take days to result), LFTs, HIV, HBV/HCV, TB, syphilis, EKG.
- Tx: agonist treatment with **buprenorphine** or **methadone** is 1st line tx for opioid withdrawal and OUD. Should be offered to **every patient with OUD**. Long-term agonist therapy for OUD decreases morbidity and mortality (BMJ 2017;357:j1550). When choosing bup vs. methadone consider long-term plan: methadone = daily observed administration at clinic. Buprenorphine = transmucosal TID vs. long acting injectable qmonth vs. subcutaneous injection q6mo prescribed by outpatient provider.
- Pain control: pts w/ OUD and/or chronic opioids likely have developed tolerance and require high doses of opioids to treat pain
  - If using non-prescribed opioids: can initiate methadone for withdrawal & add short-acting opioids titrated to pain
  - If taking methadone: give usual dose (once confirmed) & add short-acting opioids (e.g. oxycodone) titrated to pain
  - If taking buprenorphine: there are several strategies. MGH peri-operative guideline
    - For pain of short duration, may continue daily bup & add short-acting opioids (may need high doses, consider PCA)
    - Give total daily dose of bup divided 3-4x daily (e.g. 4-8mg q6-8h for mod-severe pain)
    - D/c bup & use short-acting opioids to tx acute pain. Blocking effects of bup wear off after 24-72h, so monitor for OD (initial opioid dose is higher than pt will need). After pain resolved, re-start bup (CMAJ 2016;188:1232; Annals 2006;144:127)

ACUTE OPIOID OVERDOSE (OD) (NEJM 2012;367:1372)

- Signs: ↓mental status, ↓RR, ↓tidal volume, miosis. Normal pupils do not exclude opioid toxicity → co-ingestions may be sympathomimetic/anticholinergic. Rare: hypoxic seizure. Acute toxicity is a clinical diagnosis; ⊕ tox screen does NOT confirm toxicity
- Acute stabilization: assess **airway** (**mental status**). If apnea and/or stupor, bag valve mask (with O2). Administer **naloxone**
- **Naloxone**: goal is to improve mental status, SpO2, and ensure RR>10, NOT to achieve normal level of consciousness
  - Dose: 0.4mg IV, if no response increase dose q2 min:→0.5mg→2mg→4mg→10mg→15mg. Can administer intranasally or IM
  - Effect lasts 20-40min, but most opioids last longer. **OD can recur after naloxone wears off** so may need to redose or start gtt.
  - *NB*: too much naloxone will precipitate opioid withdrawal. Consider diluting 0.4mg in 10cc saline and push 1cc q2-3min
  - If failing to respond, consider **intubation** (STAT RICU consult)
- Post-resuscitation: continuous O2 monitoring, CXR (post-OD pulmonary edema does NOT respond to diuretics, may evolve to ARDS), APAP level. Examine skin for fentanyl patch (remember fever + patch → overabsorption). Consider naloxone gtt

ACUTE OPIOID WITHDRAWAL

- S/Sx: dysphoria, restlessness/irritability, muscle twitching, yawning, piloerection, mydriasis, rhinorrhea, myalgia/arthralgia, lacrimation, n/v/d, abd cramping. Onset: 6-12h after short-acting opioids, 24-48h after last methadone, variable for fentanyl analogs (long half-life)
- Buprenorphine: **high affinity partial agonist** with lower risk of respiratory depression/OD than methadone
  - Wait until Clinical Opioid Withdrawal Scale (COWS) >10, usually 10-12h after last heroin use/short acting opioids. **Avoid precipitated withdrawal**—rapid, intense withdrawal due to displacement of full agonist by partial agonist
    - First dose: 4mg/1mg (1/2 of an 8mg/2mg bup/nal film). Second dose: if continued withdrawal sx, give another 4mg/1mg after 45-60min. Third dose: if recurrent withdrawal sx, give another 4mg/1mg after 6-12h
    - Maximum dose for Day #1 is 12mg buprenorphine (unless PDMP documented recent tolerance of higher doses)
    - Prescribe total from Day 1 for Day 2, then reassess later in the day. Can give additional 4mg/1mg for withdrawal symptoms. Max dose for Day #2 is 16mg buprenorphine
  - Microdosing (Bernese Method): start w/ small initial dose of bup (0.5mg) & incrementally increase dose & freq over 7-10d while pts continue other opioids (prescribed or recreational) until therapeutic bup dose (>8mg daily) achieved (CMAJ 2020;192:E73)
- Methadone: **long-acting full agonist**. Check and trend ECG for QTc, use with caution with other QTc-prolonging meds.
  - Day 1 initial dose: 20mg-40mg x1 (20mg dose for pt >60, c/f ↓tolerance, concurrent sedating meds/BZDs, or liver dysfnx). F/u COWS q4h. If >2h s/p first dose and COWS >12 or pt reporting w/d, spot dose 10-20mg x1. MUST call ACT if ≥60 mg daily dose
  - Day 2: Continue dose if COWS <6; incr. by 10-20mg if COWS 6-12. If not pursing methadone maintenance, consult ACT
- If unable to initiate suboxone/methadone, or if in precipitated wd, offer symptomatic medications and short-acting opioids for pain:
  - Autonomic dysreg: clonidine 0.1-0.2mg TID PRN/lofexidine 0.54-0.72mg QID PRN; avoid w/1st bup/methadone dose, watch BP
  - GI upset: Bentyl 10-20mg q6h PRN abd cramps; ondansetron 8-16 mg q8-12 PO/IV PRN, promethazine 25-50mg IM PRN N/V; loperamide 2mg PRN diarrhea
  - Anxiety: hydroxyzine 25mg q8h PRN or trazodone 50-100mg q8h PRN; if precip w/d, consider lorazepam 1-2 mg q6h PRN
- Discharge: ensure pts have **insurance**, **PCP**, **provider** to prescribe bup/nal or methadone, **list** of shelters/needle exchanges, **PrEP**
  - **Last dose letter** for patients on methadone maintenance (includes date/amount of last methadone dose)
  - **Prescribe naloxone** and **teach** OD response. Emphasize that naloxone reverses OD for ~30min. After OD → EMS to the ED
  - **Bridge Clinic**: call 617-643-8281 Mon-Fri 8am-4pm to schedule appt or present as walk-in

Richard Seeber

TOBACCO (USPSTF: JAMA 2021;325:280, ATS: AJRCCM 2020;202:e5)

Screening: Tobacco: **5A's** framework: **A**sk about use, **A**dvise to quit, **A**ssess readiness, **A**ssist if ready, **A**rrange follow up.
Treatment: Combination of counseling and medication is most effective (Cochrane Rev 2016).

- Set a **quit date**, typically in 2-4w. Abrupt cessation more effective than taper (Annals 2016;164:585).
- Counseling: Individual, group, cessation coach, telephone support lines; smoking cessation resources at MGH.
- Pharmacotherapy: **Varenicline** is first line and should be started even in patients not ready to quit (AJRCCM 2020;202:e5). For those patients planning to quit, start pharmacotherapy **1-2w prior to quit date**; continue for 3-6mo; monitor tobacco use to see decrease.
  - Varenicline: 0.5mg qd x3d → 0.5mg BID x4d → 1mg BID. SEs: nausea, insomnia/vivid dreams; avoid if hx PTSD/SI, but recommended in other comorbid psych conditions (AJRCCM 2020;202:e5); monitor for neuropsychiatric symptoms
  - Bupropion: 150mg qd x3d → 150mg BID. SEs: insomnia, agitation, HA, dry mouth. CI: seizure disorder. Relative CI: ↓GFR
  - Nicotine Replacement Therapy (NRT): long acting (patch) + short acting (lozenges/gum/nasal spray)

CANNABIS

- **Intoxication**: Euphoria followed by relaxation; tachycardia; hallucinations (especially w/ high potency THC, e.g. wax/dab)
- **Drug interactions:** Research not definitive, cannabis may increase warfarin levels (Basic Clin Pharm Tox 2019;124:28)
- **Cannabinoid hyperemesis syndrome**: Dysreg of GI cannabinoid receptors → recurrent n/v, abd pain, sx relief w/ hot showers, mild leukocytosis. **Tx**: THC cessation, IVF, antipsychotic (haloperidol), BZD, capsaicin cream (Exp Opin Pharmacoth 2022;23:693).
- **E-cigarette or Vaping Associated Lung Injury (EVALI)**: Dx of exclusion in respiratory failure <90d after e-cig/vape use. b/l GGOs; BAL with lipid laden macrophages. Possibly due to Vit E acetate (NEJM 2020;382:903). Suspected cases must be reported to MA DPH.
- **Tx:** No FDA-approved meds. Topiramate, NAC, gabapentin, dronabinol, nabilone may help cravings (Pharmacotherapy 2016:511).

SYNTHETIC CANNABINOIDS (SPICE/K2/BATH SALTS)

- **Intoxication**: Agitation/violence, hallucinations, paranoia, anxiety, tachycardia, arrhythmia, myoclonus, diaphoresis. Variable time to symptom onset and recovery based on synthetic used, quantity consumed, and route of use (inhalation, ingestion).
- **Tx**: Low stimulation environment, IVF, consider IV/IM BZD to reduce agitation and prevent seizure (Curr Psychiatry Rep 2016;18:52).

BENZODIAZEPINES

- **Intoxication:** Memory impairment, disinhibition, psychomotor slowing, depression, amplified w/ EtOH.
- **Withdrawal**: ↑Anxiety, irritability, tremor, HA, nausea, autonomic instability, photo/phonophobia, seizures, paranoia, hallucinations, depersonalization, and delirium. Duration depends on half-life of agent, ranges from 2-10d (NEJM 2017;376:1147). **Can be lethal.**
- **Abstinence syndrome weeks after cessation**: Anxiety, tachycardia, restlessness.
- **Tx**: Manage severe w/d inpt (see *Alcohol Withdrawal*). Consider taper w/ same BZD. Consider collab w/ outpt prescribers

Commonly Used BZDs	~ Equiv Dose	Half-life (hours)
Alprazolam (Xanax)	0.5mg	6-27 (oral peak 1-2)
Chlordiazepoxide (Librium)	25mg	5-30 (oral peak 0.5-4)
Clonazepam (Klonopin)	0.25mg	18-50 (oral peak 1-2)
Diazepam (Valium)	5mg	20-50 (oral peak 0.5-1)
Lorazepam (Ativan)	1mg	10-20 (oral peak 2-4)
Temazepam (Restoril)	10mg	3-19 (oral peak 1-2)

STIMULANTS: COCAINE, METHAMPHETAMINE, PRESCRIBED STIMULANTS

Cocaine:

- **Intoxication**: Euphoria, hyperactivity, grandiosity, anorexia, anxiety, psychotic sx (formication, paranoia, AH/VH). ½ life ~1h.
- **Withdrawal**: Depression, fatigue, nightmares, cravings,↑sleep/appetite. Acute w/d tx: Supportive care, BZD if symptoms severe.
- **Complications**: *Acute*: vasospasm, HTN emergency (**Tx**: BZD, phentolamine if refractory, nitroglycerin; avoid βB), ACS (**Tx**: ASA, nitro, BZD), arrhythmia, ischemic bowel. *Chronic*: LVH, cardiomyopathy (NEJM 2001;345:351). Intranasal: nasal septum perforation, ulcers, chronic rhinitis. Inhalation: cough, SOB, hemoptysis, PTX. "Cocaine-Induced Lung Injury": syndrome of fever, hemorrhagic alveolitis, respiratory failure, eosinophilic infiltration thought d/t levamisole additive. Injection: discuss harm reduction practices, eg using vitamin C powder as acidifier over lemon juice (fungal infxn) or vinegar (damages veins), use PCOI guide and Grayken guide.

Methamphetamine:

- **Intoxication:** Similar to cocaine. Sympathetic activation, executive dysfunction, memory impairment, ↑libido. ½ life ~6-12h.
- **Complications:** HTN, hyperthermia, rhabdomyolysis, may exacerbate existing psych sx. **Tx for severe agitation**: BZD first line.

Stimulant Use Disorder Tx: Consult ACT. Limited psychosocial programs in community and mixed evidence for pharmacotherapy.

- **Psychosocial**: Contingency management is best supported; also consider CBT, community reinforcement, motivational interviewing.
- **Pharmacotherapy:** No FDA approved meds. Insufficient evidence for replacement therapy, opioid agonists or NAC across all stimulant use disorders (PLOS ONE 2020;15: e0234809). Replacement therapy may help sustain cocaine abstinence (Cochrane Review 2016). Consider topiramate and/or baclofen for cocaine cravings/dependence (Psychiatry 2005;2:44). IM ER naltrexone + PO ER bupropion may reduce meth use (NEJM 2021: 384;140).

HALLUCINOGENS

MDMA/Ecstasy: Intox: Euphoria, HTN, hyperthermia, stimulant properties. ½ life ~2h. **Complications**: HypoNa, serotonin synd, seizure
LSD: Intox: Euphoria, synesthesia, depersonalization. **Complications**: Frightening imagery. Rare vital sign abnormalities.

XYLAZINE (TRANQ)

- **Intoxication:** α2 agonist found as adulterant, thus most overdoses are concomitant with fentanyl. Bradycardia, resp depression, hyperglyc, miosis, hypothermia, PVCs, transient HTN → sustained hypotension. ½ life ~23-50min **Tx:** No specific reversal agents for humans. Treat concomitant opioid OD. (Addiction 2024;119:606)
- **Xylazine wounds**: necrosis w/ black eschar. **Tx:** Standard wound care.

CIVIL COMMITMENT FOR SUBSTANCE USE DISORDER TREATMENT (Section 35 in MA - MGL ch.123 §35)

Process by which the court may involuntarily commit someone to inpatient SUD treatment when there is immediate likelihood of serious harm as a result of the SUD. Petition must be filed by MD, blood relative, spouse, guardian, police officer, or court official.

Psychiatry

Drug Testing

MGH Toxicology Screens

- **Basic serum toxicology screen**: Quantitative assay for EtOH, salicylates, acetaminophen; qualitative assay for TCAs.
- **Urine drug screen** (VDAU): Qualitative screen for amphetamines, BZDs, cocaine, opiates, fentanyl, oxycodone. *Not included*: **THC,** bupe, barbituates, methadone, meperidine, LSD, PCP, propoxyphene. If a patient may need a THC test (often needed for transfers to facilities such as McLean or if ordering w/u for depression, mania, psychosis), please include in original utox order
- **SUD management panel** (VPP2): Same as VDAU + bupe, methadone (24h turn-around).
- **Oral drug screen**: Amphetamines, buprenorphine, benzos, cocaine & metabolite, opiates, methadone, oxycodone, 6-MAM, fentanyl

Test	Turnaround
Serum tox	2 hours
Urine tox	2 hours
SUD	2-24 hours
Oral tox	2-3 days

Oral vs. Urine Tests

- **Oral drug mass spectrometry**: Used for outpatient testing for chronic opioids or buprenorphine. Differentiates BZD subtypes and opiates. Superior sensitivity/specificity of amphetamines, opioids and cocaine. More expensive than UTox screen.
  - ODS technique: Rinse w/ 40 mL water for 30 seconds and swallow prior to test, repeated twice. Wait 10 minutes (early testing → false negative), then place swab under tongue.
- **Urine drug screens:** Cheap, easy, noninvasive. Used more often on inpatient. Does not differentiate subtypes of BZDs or opiates. Superior sensitivity for BZDs but does not detect lorazepam. Superior sensitivity for buprenorphine (detects doses as low as 2mg/d). **THC, barbiturates, and 6-MAM must be ordered separately.**
  - Tampering: More common w/ UDS (e.g synthetic urine, smuggling/storing urine in bathroom)

Strategies to minimize UDS tampering: direct observ, check specimen cup temp, ask pts to leave belongings outside bathroom

Detection Time of Drugs in MGH Toxicology Screens*		
	Urine	**Oral**
Urine Tox Panel (VDAU)		
Amphetamine, methamphetamine	1-3 days	3-6 days
Benzodiazepines		
Alprazolam	2-3 days	1-2 days
Chlordiazepoxide	10-20 days	5-10 days
Clonazepam	5-10 days	5-10 days
Diazepam	10-20 days	5-10 days
Lorazepam	Not detected	1-2 days
Cocaine	2-5 days**	2-7 days**
Opiates (morphine, codeine)	2-4 days**	2-4 days**
Hydrocodone, hydromorphone	2-3 days	2-3 days
Fentanyl	2-3 days***	2-3 days***
Oxycodone	-2-3 days	2-3 days
Urine SUD Panel		
Buprenorphine	2-3 days	6-10 hours
Methadone	5-10 days	5-10 days

*Estimates updated 3/2023 from MGH laboratories (James Flood, PhD and Sacha Uljon, MD PhD) Detection times are specific to MGH and are not hard cut-offs.
**Longer in chronic/high-dose users
***Best available estimates (detection time for chronic/high-dose fentanyl users over long period of time is unknown)

		Drugs Detected	False Positive	False Negative	Comments
Urine Tox Panel (VDAU)	Amphetamines	Amphetamine, methamphetamine, ecstasy/MDMA	Beta blockers, ranitidine, bath salts, trazodone, bupropion		Ritalin does not cause a false positive
	Benzos	Alprazolam, chlordiazepoxide, clonazepam, diazepam, triazolam		Lorazepam, temazepam	Clonazepam detected even at 1mg/day
	Cocaine metabolites	Benzoylecgonine	*None*		
	Opiates	Morphine, hydromorphone, codeine, hydrocodone, heroin	Poppy products, rifampin, levofloxacin	Oxycodone, oxymorphone	Fentanyl, methadone, naloxone, naltrexone do not interfere
	Fentanyl	Norfentanyl (metabolite), fentanyl			
	Oxycodone	Oxycodone and metabolite oxymorphone		Substances imparting color to urine (e.g., Flagyl)	
Urine SUD Panel	Buprenorphine	Parent drug and major metabolite			
	Methadone	Methadone	Quetiapine, tramadol, vortioxetine, chlorpromazine		Does not cause false positive for opiates

SOURCE: MGH TOXICOLOGY LAB AND PCOI

Interpreting Results

Tox screens alone should not be used to dx SUDs as they do not give information on frequency or intensity of use. False positives and negatives are possible. It is not recommended to alter prescribing meds based on positive tox screens; instead, use these tests to check for concomitant substance use, monitor opioid use, and initiate conversations around use with patients. The best tox screen is a respectful history.

Primary Care Health Screening & Maintenance

General Screening Guidelines [Evidence Grade] ([a]USPSTF, [b]ADA, [c]AACE, [d]ACC/AHA, [e]ACCP, [f]ACS)

Age	18	19	20	21	25	30	35	40	45	50	55	60	65	70	75+
Cardiovascular Screening/Preventative Health Recommendations															
CVD Risk	Assess RFs Q4-6y [B][d] (age, sex, Tchol/HDL, HTN, DM, CKD, smoking, FHx)								Estimate risk w/ ASCVD calculator Q4-6y [B][d] If ASCVD risk ≥10% prescribe a statin* [B][a] *If ASCVD risk 7.5-10% consider statin [C][a]. Insufficient evidence for/against statin for age >75 [I].[a]						
						PREVENT risk calc (30-79y) will soon replace the above. Provides 10yr and 30yr risk. Race free. Includes eGFR/UACR, BMI, A1c, and zip code (proxy for SDH)								
ASA for 1° ppx									Consider in 40-59y w/ ASCVD risk ≥10% w/ no ↑risk of bleeding[δ] [C][a,d]				Not rec for adults >60 [D][a]		
DM	If HTN or BMI ≥25 (≥23 Asian) w/ ≥1 DM RF^, or GDM [B][b]								Fasting plasma glucose or A1C [B][b] Screen minimum Q3y. ↓interval if abnl result or new RF (e.g. weight gain) [C][b] ✓ annually in pre-DM[b]						
HTN	Q3-5y; Q1y if elevated BP reading, obese, AA [A][a]								Q1y [A][a]						
HLD	Insufficient evidence for screening [I][a]		Men 20-45, women 20-55: screen Q5yr, ↑ if RF [C][c] Q1y in DM [B][c]							M >45, F >55 Q1-2y if no RF* [A][c], Q1y in DM [B][c]			Screen Q1y [A][c]		
Obesity	Annual BMI [C][d] → refer for or offer comprehensive lifestyle program if ≥25 (see *Weight & Weight Loss*) [B][d]														
Diet	Intensive behavioral counseling if CVD RF* [B][a]														
Exercise	150min/wk moderate-intensity exercise or 75min/wk intense-exercise & 2d of muscle strengthening activity [A][d]														
Universal Cancer Screening															
Colorectal CA	Start 10y prior to age of affected family member at dx**								45-49 needs colo Q10y, flex sig Q5y,or FIT testing Q1y [B][a] ; if flex sig or FIT abnx, will need colo. If colo abnx, path determines f/u						+/-**
Lung CA										(Age 50-80) Q1y low-dose CT if 20 pack-yrs or more (regardless of quitting date) or if current smoker [B][a]***					
Infectious Disease Screening															
HIV	Screen all age 15-65 at least once; repeat based on risk assessment [A][a]														
HCV	Screen all 18-79 at least once; repeat based on risk assessment [B][a]														
HBV	Born in endemic region, getting HD or immunosuppressed, HIV+, IVDU, MSM, close contact w/ HBV+ person [B][a]														
Latent TB	Screen if born or lived in high risk country (see USPSTF recs) or high risk setting (homeless, jail) [B][a]														
Syphilis	Screen in all individuals at increased risk of infection [A][a]														
Psych/SUD/Social Risk Factor Screening															
Depression	Q1y [B][a] by PHQ-2: in 2w how often (a) little interest/pleasure doing things & (b) down/depressed/hopeless (JAMA 2020;323:2290). Not enough evidence to recommend for or against screening for suicide [I][a]														
Anxiety	Screen regularly in adults ages 19-64, various screening tools such as GAD-2 or GAD-7 [B][a]														
Alcohol	Screen regularly with AUDIT-C [B][a]														
Tobacco	Every encounter [A][a]. **A**dvise to quit, **A**ssist doing so (plan, quit date, QuitWorks, meds), **A**rrange f/u. Strong evidence to start varenicline (Chantix) over other tx options, despite psych comorbidities or readiness (AJRCCM. 2020;202:e5)														
Unhealthy Drug Use	Screening [B][a] via asking questions about unhealthy drug use (not drug testing) is beneficial when services for accurate diagnosis, effective treatment, and appropriate care can be offered (JAMA 2020;323:2310)														
Inter-partner Violence	Screen regularly in women of reproductive age [B][a]. Use HITS tool. Assess immediate safety & consider HAVEN referral. ↑ rates in LGBT population.										Consider screening for ongoing IPV, elder abuse screening [I][a]				
Fall Risk												Yearly screening, PT, Vit D [B][a]			

*If ASCVD borderline risk (5%-7.5%), use risk-enhancing factors [FHx, LDL-C ≥160, metabolic syndrome, CKD, S. Asian race/ethnicity, chronic inflammatory disease including HIV, menopause <40y, pre-eclampsia or pre-term delivery, abn biomarkers (e.g. hsCRP, Lp(a), apoB, ABI)] or coronary artery calcium score to guide decision about statin (see *Outpatient CV Health*)

[δ]History of previous GIB or PUD or bleeding from other sites, thrombocytopenia, coagulopathy, CKD, and concurrent use of other medications that increase bleeding risk (NSAID, steroids, DOACs, Warfarin)

^DM RFs: prior abnl testing (A1c≥5.7), FHx, AA/Latinx/Asian/NA ancestry, Hx GDM, PCOS, CVD, HTN, HDL<35 or TG>250, physical inactivity, other conditions associated w/ insulin resistance (e.g. obesity)

**Begin at age 40 or 10y prior to earliest dx in fam (whichever comes first) for ≥1st degree relative dx<60 or two 1st degree relatives of any age; Age 40: ≥1st degree relative dx≥60; 75+: based on life expectancy. Early screening for special populations: hx of high-grade polyp, IBD, prior colon or rectal ca, hx prior pelvic/gut radiation, genetics.

***Consider screening cessation if limited life expectancy or screening would impede surgical candidacy.

Additional Screening Guidelines for Men [Evidence grade] ([a]USPSTF, [f]ACS, [g]Endo, [h]PCOI)

Age	18-40	40	45	50	55	60	65	70	75+
AAA							If +tobacco hx [B][a *]		
Prostate CA,***		Discuss risk-benefit if FHx** Q1-2y[δf]	Disc. risk-benefit if FHx***, AA Q1-2y[δf]	Discuss risk-benefit if Q1-2y[δ] if life expectancy ≥ 10y[f]					
					PSA 55-69y if pt preference [C][a], *recommend against* if >70y [D][a]				
Testicular CA	*Recommend against* routine screening in all men[Σ] [D][a]								
Anal CA[#]	In MSM: anal Pap smears Q1y if HIV+ (space to Q3y after 3 neg Paps); consider Q2-3y if HIV-[h]								
Osteoporosis				If RF^[g]				DXA[g]	
STIs	In MSM: Q1y, Q3-6mo if multiple/anonymous partners or sex in conjunction w/ drug use; hx re: sexual practice can guide screening (pharyngeal, anal, urine). Prescribe PrEP to patient at risk of HIV acquisition [A][a]								

*Society for vascular surgery recommends screening in men and women **Inform all patients of uncertainties, risks, and potential benefits before starting PSA screening

***Discrepancy between societal guidelines, USPSTF: individual risk-benefits discussion for persons with prostates aged 55-69 [C], stop screening at age 70 [D]. ACS: for average-risk persons with prostate, start risk-benefits discussion at age 50, stop when life expectancy <10 years

[δ]Screening frequency varies based on level. PSA < 2.5ng/mL = Q2y. PSA ≥ 2.5ng/mL = Q1y[f]; Amer Urological Assoc recs Q2y interval

**>1 first-degree relative with history of prostate cancer at early age ***First-degree relative diagnosed with prostate cancer at age <65

^Low body weight, prior fracture, smoking [Σ]If higher risk (h/o cryptorchidism or orchiopexy, testicular atrophy, or sxs), evaluate, educate & consider periodic testicular exams

Primary Care — Health Screening & Maintenance

#Lacking evidence to inform screening initiation age & intervals. NYS DOH AI includes follow-up algorithm. Stop when life expectancy <10y

Additional Screening Guidelines For Non-Pregnant Women [Evidence grade] ([a]USPSTF, [f]ACS)

Age	18	19	20	21	25	30	35	40	45	50	55	60	65	70	75+
Breast CA*	Consider BRCA counseling if +FHx. Screening tools available [B][a]							Q1-2y mammogram age 40-74. Stop if <10y life expectancy [a,f]							
Cervical CA^δΣ					Q5y 1° high risk HPV testing (preferred if available); if not available, Q5y cytology + hrHPV co-testing OR Q3y cytology alone[f]								If neg adequate screening, stop		
				Q3y cytology [A][a]		Q5y 1° hrHPV testing (preferred)[f] OR co-testing (hrHPV & cytology) OR Q3y cytology alone [A][a,f]									
Ovarian CA	*Recommend against* routine screening in asx women [D][a] (Lancet 2021;397:2182)														
STIs	≤24: GC/CT annually [B][a]					Screen based on risk assessment [B][a]									
Contraception	Discuss with everyone including trans ♂ (see *Women's Health* for contraception guidelines). Start folic acid at reproductive age if planning/capable of pregnancy [A][a]														
Osteoporosis	Consider earlier screening based on FRAX assessment [B][a] (*see Osteoporosis*)												DXA [B][a]		

*Discrepancy btw societal guidelines despite same evidence. USPSTF: 40-74 Q2y [B]; >75 no recommendation [I]. ACS: 40-44 option to start Q2y screening; 45-54 Q1y; ≥55 discuss transitioning to Q2y screening until life expectancy <10y. ACOG: offer mammography at 40; start screening at 50; discuss cessation at 75; screen Q1-2 years

^All screening methods still accepted to promote access to adequate cervical cancer screening. USPTF recommends age 21 start whereas ACS recommends age 25. ACOG recommends start at age 21 due to underscreening in younger populations.

δWomen w/ HIV require more frequent Paps & Paps preferred (HPV testing w/o cervical cytology is **not** approved). See NIH guidelines

ΣSubsequent screening dictated by age, prior screening results, and other factors. Use ASCCP Web App for algorithm of next steps.

Additional Screening Guidelines For Transgender Individuals*

Age	18-40	40	45	50	55	60	65	70	75+
CVD Risk	As above; if patient has been on hormones for many years, use hormonal sex in the calculator								
Osteoporosis	Consider at any age if s/p gonadectomy and >5y w/o hormone tx			Consider based on FRAX (no guideline on which sex to use)			DXA		
Breast CA				Trans ♀: Q2y *after* 5-10y hormone use					
	Trans ♂: if natal tissue present (incl s/p partial mastectomy), screen per guidelines for non-trans ♀								
Cervical CA	Trans ♂: if natal tissue present (incl s/p subtotal hysterectomy), screen per guidelines for non-trans ♀^								
Prostate CA	Trans ♀: screen per guidelines for non-trans ♂. Use lower ULN for PSA if on estrogen								

*See Transgender Health

^Cells more likely to be "unsatisfactory" for interpretation on testosterone. On order, note that pt is on testosterone and/or amenorrheic. Self-collected vaginal swabs as sensitive as provider-collected swab (PLoS 2018;13)

Vaccines (CDC, [a]NYS DOH AI)

Immunizations	19-21	22-26	27-49	50-64	≥65
COVID-19	1 or more doses of updated (2023-2024) formula				
Influenza	Annual flu vaccine				Annual high dose flu vaccine
	No live (intranasal) if immunocompromised (or contact), pregnant, asplenia, cochlear implant, CSF leak, ≥50; OK for 65+ to get regular adult flu vaccine if high dose not available				
Tdap/Td	1 dose Tdap then Td or Tdap booster every 10 years; extra Tdap dose during each pregnancy				
RSV	Seasonal administration in pregnancy				Recommended for adults 60+
MMR*	1-2 doses based on indication (if born 1957 or later)				
	1 dose in ♀ of childbearing age; 2 doses if HIV & CD4≥200, healthcare personnel, or college students				
Varicella*	2 doses (if born 1980 or later)				
Zoster*	Immunocompromised: 2 doses of RZV 1-2 mo apart			All: 2 doses of RZV 2-6 mo apart	
	Administer RZV regardless of history of Zostavax (live, no longer available) administration				
HPV**	2-3 doses		27-45y SDM***		
	3 dose series to all people with HIV up to 45y[a]				
PCV15/PPSV23 OR PCV20	Chronic heart, lung, kidney, or liver dz; DM; AUD; smoking; nephrotic syndrome; CSF leak; cochlear implant; immunocompromising conditions: PCV20 x1 OR PCV15 x1 followed by PPSV23 x1 ≥ 8 wks or 1 yr later				If never vaccinated, PCV20 x1 OR PCV15 x1 followed by PPSV23 x1 ≥1 yr later. If partially/fully vaccinated before age 65, may need to repeat vaccine. See CDC website for full details.
Hep A	Travel to endemic country, HIV, MSM, **any** drug use (not just IVDU), chronic liver dz, undomiciled, work w/ HAV, close contact to international adoptee, settings for exposure, pregnancy at risk for infxn: 2 doses				
Hep B****	Universal vaccination for adults ages 19-59, as well as adults 60+ with risk factors for HBV (travel to endemic country, HCV, HIV, sexual exposure risk, IVDU, chronic liver dz, incarcerated, mucosal or percutaneous blood exposure (incl dialysis, DM, work exposure) Recombivax HB: 3 doses (dose doubled if pre-dialysis or on HD); HEPLISAV-B: 2 doses				
Meningococcus** (MenACWY/MenB)	Functional/anatomical asplenia, HIV, ↓complement (including by meds), travel to endemic country, freshmen in dorms, military recruits 1-2 doses + Q5Y if risk remains (add MenB for asplenia, ↓complements + Q2-3Y if risk remains)				
Hib	Functional or anticipated asplenia: 1 dose (if no prior); after HSCT: 3 doses (regardless of vaccination hx)				
Monkeypox	Any person at risk of monkeypox (persons who are gay, bisexual, and other MSM, transgender or nonbinary people who in the past 6 mo. have had a new STD dx or >1 sexual partner): 2 doses				

*Hold live vaccines in pregnancy, malignancy, and immunocompromised (incl HIV w/ CD4 <200, cochlear implant). Ok if CD4 ≥200

**Wait until after pregnancy ***Shared decision making (SDM): most likely to benefit adults not yet exposed to HPV or w/ new sex partners

****Conduct complete serologic testing (HBsAg, anti-HBs, and anti-HBc) on all adults over 18 at least once in a lifetime. Boosters not recommended for most people who have been vaccinated. For patients on HD, if anti-HBs <10 mIU/mL, a booster should be administered. For other immunocompromised people (HIV, stem-cell transplant recipients, chemotherapy) the need for booster doses is undetermined. Also consider booster in patients with anti-HBs levels <10 mIU/mL with an ongoing risk for exposure.

Miriam Singer

GENERAL CONSIDERATIONS (NEJM 2019;381:2451)

Gender Terminology

- Gender identity: a person's sense of one's gender; can be congruent with or differ from sex assigned at birth
- Transgender/trans: a person whose gender identity is different from cultural expectations based on their sex assigned at birth vs cisgender: sex assigned at birth and gender are congruent
- Non-binary, gender non-conforming, genderqueer: a person whose gender identity does not fall within the traditional gender binary. People who are non-binary may see themselves as being both male and female, neither male nor female, or as completely outside of or unrelated to these categories

History: use "Sexual Orientation/Gender ID" and "Demographics" activities in EPIC to update patient header w/ chosen name/pronouns

- Gender identity data: name and pronouns, gender identity + sex assigned at birth
- Organ inventory: guides screening and physical exam. Note natal and surgical anatomy. Confirm patient's preferred terms for organs
  - Screening: per usual guidelines based on organs present; Consider past/present HRT use; ex): trans women screen breast CA if >50yo and 5yr HRT
  - Include present organs in ddx: e.g., PID, fibroids, endometriosis in trans M w/ uterus/fallopian tubes; prostatitis in trans F
- Sexual history: "What body parts do your sexual partners have?" "What body parts do you use for sex?" "What terms do you use to refer to your body parts?"
  - Use gender neutral language to use for natal parts (i.e., chest wall instead of breast, monthly bleeding instead of menses)
  - Self-collected rectal, oropharyngeal and vaginal swabs as sensitive as provider-collected swabs for STIs and HPV (Cyto 2019;63); useful for individuals who want to avoid an invasive exam
  - Offer HPV, HBV vaccine series; CDC primary prevention guidelines
  - Consider HIV PrEP for patients who use IV drugs or have multiple sexual partners: (AETC prescriber guidelines)

Physical Exam Considerations

- Skin: acne, hair, irritation/infection 2/2 chest binding or penile/scrotal tucking, tattoos at potential skin flap sites, silicone injections
- Abd: complications from tucking include prostatitis, cystitis, epididymo-orchitis,
- GU: pelvic exam in trans M can be traumatizing and painful 2/2 vaginal atrophy on testosterone. Tips: 1-2w vaginal estrogen before exam; pediatric speculum; trauma-informed care esp physical exam; consider PO benzos 1h before; self-swab if possible.

GENDER-AFFIRMING CARE (WPATH Standards of Care; Trans Line; MGH Transgender Health)

Gender dysphoria: distress a person feels due to a mismatch between their gender identity and their sex assigned at birth

- Affirm gender identity and explore options below for expression of identity and alleviation of gender dysphoria
  - Psychotherapy: safe space to explore gender expression, impact of internalized transphobia, social support, body image, strategies for resilience. Not required to pursue hormone tx or surgery
  - Changes in name and gender marker on identity documents; voice and communication therapy; hair removal; chest binding or padding; genital tucking or packing; padding of hips or buttocks; hormone tx; surgery

Hormone therapy: initiate w/ informed consent & shared decision making w/ patient (WPATH standard, Endocrine Reviews Feb 2019,40,97-117)

- Anticipatory guidance: full effects can take 1-5y. Dose titration requires frequent labs and visits in the first year
- Feminization**:** 17-beta estradiol (PO/SL, transdermal patch, IM) + androgen blocker (spironolactone/leuprolide)
- Masculinization: Testosterone (topical gel/transdermal patch, IM/SQ). Progestins, Aygestin early on may help stop menses
- Fertility: Discuss fertility preservation (egg/embryo freezing, sperm banking) before starting tx
- Testosterone ≠ contraception. If partner makes sperm, discuss birth control: pills, patches, Nexplanon and IUD are all options
- When monitoring treatment, indicate hormonal sex in lab requisition and interpret values using ranges for hormonal, not natal sex.
- Reasonable to provide 1-6 mo of bridge Rx if patient is already on hormones and then refer to another provider who can prescribe.

	Contraindication	Potential Risks	Irreversible changes	Reversible changes	Monitoring
MtF	Absolute: estrogen-sensitive neoplasm, ESLD	- VTE^ (HR 1.9) - Gallstones - ↑TG, LFTs - HTN - ↑prolactin - Migraines	- Chest growth - ↓ testicular volume	- ↓muscle mass - fat redistribution - hair/skin softens - ↓sex drive - ↓libido, erections	- If spironolactone: BP, BMP baseline and q3 mo, then q1y - total T, E q3-6mo until at goal, then q1y - prolactin PRN if sxs
FtM	Absolute: ACS, polycythemia (Hct >55%), pregnancy, sex hormone sensitive neoplasm	- Erythrocytosis - HLD, ↑liver enzyme - Sleep apnea	- Deepening of voice - ↑ facial and body hair - Clitoromegaly - Vaginal tissue atrophy - Scalp hair loss**	- menses cessation - ↑ sex drive - ↑ muscle mass - acne	- Before tx: urine HCG - CBC q3mo, then q1y - total T q3mo, then q1y

^Strongly encourage smoking cessation to attenuate risk. Consult UCSF guide for risk-benefit analysis after VTE. Transdermal route may ↓VTE in age >45 or previous VTE **Treatment with 5-alpha reductase inhibitors may reverse some testosterone effect

Surgery: may require 6 mo hormone tx first and support letter from two mental health providers (depends on surgery type). If removing gonads, establish bone mineral density w/ DEXA.

- Feminization**:** vaginoplasty, mammoplasty, voice feminization surgery, thyroid cartilage reduction, penectomy, orchiectomy
  - Pre-op: no evidence to stop hormone therapy in otherwise low-risk transgender women, electrolysis for hair removal
  - Post-op considerations: tissue necrosis, fistulae, urethral stenosis, UTIs, anorgasmia; regular vaginal dilation/penetrative intercourse to maintain vaginal depth and width
- Masculinization: mastectomy, phalloplasty, metoidioplasty, scrotoplasty, hysterectomy, oophorectomy
  - Post-op considerations: tissue necrosis, urinary tract stenoses/fistulae, flap loss

BREAST CONCERNS (PCOI – Breast Concerns)

Most breast concerns seen in primary care are benign (~90%); evaluation should focus on ruling in/out malignancy.

- Nipple Discharge: **Bilateral/milky:** eval bHCG, prolactin, Cr, TSH, med review. **Unilateral, bloody** (associated with mass)**:** <30y U/S, ≥30y dx mammo and U/S. Surgery referral for concerning imaging, MRI vs surgery refer if imaging negative
- Palpable Mass: All palpable masses require imaging. <30y U/S; ≥30y diagnostic mammo and U/S. Next steps pending imaging. Common ddx: fibroadenoma, cyst, galactocele, breast CA, fat necrosis
- Breast Pain: If **palpable mass** -> image. **Cyclical:** wait two cycles. **Focal**: <30y U/S, ≥30y U/S and BL dx mammo; **Diffuse**: unlikely malignant, <30y sxs management (APAP, NSAID, hot/cold, eval for extramammary causes), ≥30y BL dx mammo

VULVAR/VAGINAL CONCERNS (Obstet Gynecol 2020;135:e1; Obstet Gynecol 2020;136)

	Presentation	Dx	Tx
Vaginitis	**Bacterial vaginosis (BV)**: most common; malodorous discharge, often asx; RF = sexually active, douching Recurrent vaginosis defined as: ≥3x/yr	Wet prep or "Genital culture female" (collect vaginal swab w/ rayon swab); Gram stain: Nugent score 7-10 = BV Amsel's criteria (≥3): 1) homogeneous, thin, grey-white discharge 2) >20% clue cells 3) +KOH test 4) pH >4.5 (less reliable if post-menopause)	**Metronidazole** PO 500mg BID x7d or vaginal 0.75% x5d, clinda PO 300mg BID x7d or vaginal 2% x7d Recurrent: Metrogel x7d, followed by 2x/w maintenance for 4-6 mos
	Candida: curd-like discharge, no odor, pruritus, vulvar erythema ± edema, dysuria, dyspareunia Complicated: severe sx, pregnancy, non-*c. albicans* Recurrent defined as: ≥4x/yr	"Genital culture female" or yeast culture for fungal sensitivity if recurrent. pH normal (3.5-4.5), KOH microscopy Recurrent: test for DM2, HIV, fluconazole resistance, non-*c. albicans* infect	**Fluconazole** 150mg PO x1, miconazole 2% x7d if pregnant Complicated: Fluc 150mg q72h x3 doses Recurrent: Fluc 150mg q72h x3 doses + maintenance or fluc 150mg x 7-14d
	Other infections: Trichomonas, Gonorrhea, Chlamydia, HSV; See *STI.* If + STI, consider expeditated partner treatment. **If collecting samples at MGH, at least 3 separate swabs should be sent: G/C, genital culture (rayon), trichomonas**		
Painful	**Vulvodynia**: general or local pain, provoked or unprovoked, >3-6mo	Q-tip test to localize pain, exclude other etiology	Pelvic PT, TCA, gabapentin, lidocaine 5% before sex, steroid/lidocaine inj., sitz bath
	Genitourinary Syndrome of Menopause: vaginal dryness; pain w/ intercourse; thin, pale mucosa	Wet Mount/ Gram stain: Vaginal pH >4.5, parabasal cells	Topical vaginal estrogen, lubricants, Replens moisturizer, ospemifene
Dermatoses	• **Contact dermatitis**: erythema, swelling, fissures, erosions → r/o candida, remove offending agent • **Lichen simplex chronicus**: intense pruritis + lichenified plaque → antihistamines, topical corticosteroids; stop itch/scratch cycle • **Lichen sclerosus**: onset 50-60s, pruritis, irritation, dysuria, dyspareunia; perianal or vulvar white, atrophic papules lead to skin thinning, labia minora fusion, & clitoral hood phimosis. 5% incidence malignancy → bx to confirm; clobetasol 0.05% taper (qd x4w, qod x4w, 2x/w x4w), vulvar hygiene, monitor for SCC • **Lichen planus**: onset 50-60s, pain/burning, "purple, papular, pruritic," white lacy striae, vaginal involvement, ↑SCC risk → bx to confirm & r/o malignancy; high potency steroids, monitor for SCC		

URINARY INCONTINENCE (Obstet Gynecol 2015;126; PCOI)

- Types: **stress** (leakage w/ cough, laugh), **urge** (leakage w/ urge), **mixed** (stress + urge), **overflow** (incomplete emptying, constant dribble), **functional** (impaired mobility/cognition/neurologic); DDx: UTI, vaginal atrophy
- History: systemic sx (fevers, dysuria, pain), meds (anticholinergics, diuretics, etc.), comorbid conditions (DM, CHF), bowel habits (constipation), caffeine/EtOH use, voiding diary, multiparity is RF
- Exam: check for prolapse, vulvar/vaginal atrophy, cough/valsalva stress test; rectal exam (fecal impaction, sphincter tone); neuro exam; Dx: UA/Cx, PVR (abnl >150cc); urethral mobility assessment and urodynamic studies if etiology unclear
- Initial tx: bladder training (timed voiding), lifestyle interventions (e.g., wt loss, ↓fluid/caffeine intake), pelvic floor exercises (e.g. Kegels; pelvic floor PT). *Stress/mixed*: pessary, vaginal estrogen (for vaginal atrophy), surgery. *Urgency:* antimuscarinics (many SE), β-agonists (e.g. mirabegron) – monitor for urinary retention
- Refer to Urogyn if: hx surgery/radiation, c/f mass/pain/prolapse, no response initial tx, abnl PVR, pessary/surgery/intravesicular botox

MENOPAUSE (J Clin Endo Met 2015;100:3975)

- Amenorrhea x12mo w/o alt etiology (no need to ✓labs, can help s/p hysterectomy), avg onset at 51, suspect 1° ovarian insuff if <40
- **Vasomotor sx** (hot flashes): Systemic hormones (estrogen + progestin, estrogen mono-Rx if hysterectomy) first line if <60yo, <10y since onset & <5y duration. Avoid if: hx or >10% risk CVD, hx/high risk of breast CA/endometrial CA, hx VTE/CVA/TIA, active liver disease, unexplained vag bleeding, +smoking. Side effects: breast tenderness, vag bleeding; ↓CRC, fracture risk; ↑breast CA, CVD, VTE (equivocal if ↑risk attenuated with topical Tx); no mortality risk after 5-7y on therapy (JAMA 2017;318:927). If not eligible/desiring systemic hormones: SSRI/SRNIs (paroxetine best), gabapentin, clonidine.
- **Vaginal/vulvar sx** (now called **genitourinary syndrome of menopause**): see above; oral therapy not effective, use topical
- **Psych sx**: sleep disturbance, poor concentration**,** new-onset depression. May improve with Rx for vasomotor sx

2° Amenorrhea (AFP 2019;100:39)

- Definition: cessation of regular menses for 3mo **or** cessation of irregular menses for 6mo]
- Hx: wt Δ, diet/exercise, hot flashes, galactorrhea, hirsutism, stress, systemic illness; Initial labs: **HCG**, FSH, LH, E2, TSH, PRL
- DDx: pregnancy, hypothalamic (eating disorder, excess wt loss/exercise, stress, prolonged illness), pituitary (hyperprolactinemia 2/2 adenoma, mass effect, meds, breastfeeding, apoplexy), ovary (1° ovarian insufficiency, PCOS), uterine (prior instrumentation → scar = Asherman Syndrome), other (hypo/hyperthyroidism, DM, celiac, excess androgens [exogenous, Cushing's])
- If nl/low FSH, consider progestin challenge: medroxyprogesterone acetate 10mg x10d. If no withdrawal bleed, suggests uterine abnl

Polycystic Ovary Syndrome (PCOS) (Obstet Gynecol 2018;131)

- Affects 5-10% of women of reproductive age; often comorbid w/ CVD, DM, HTN, NAFLD, HLD, OSA, depression and anxiety
- **Rotterdam Criteria** (need 2/3): 1) oligo/anovulation, 2) clinical/biochemical hyperandrogenism, 3) polycystic ovaries on pelvic U/S
- Workup: exclude other dx (hCG, 17-OHP [pre-8AM], prolactin, TSH); DHEAS, total testosterone, SHBG to confirm if dx unclear
- Tx: wt loss, exercise, **C-OCP** (2nd line = oral progesterone or levo-IUD), spironolactone, metformin (if insulin resistant), fertility referral

Preconception Counseling/Infertility (Fertil Steril 2021;116)

- Preconception counseling (PCOI): multivitamin qd w/ 400-800mcg folic acid; review immunizations (Rubella, Varicella, HepB, COVID-19, RSV at 32-26 wks of pregnancy); optimize mgmt of wt, thyroid (TSH goal 0.5-2.5, recheck after conception), HTN (avoid ACEi/ARB, check b/l Cr, spot Ur protein/Cr), DM (↑risk birth defects; metformin/insulin first-line), mood (avoid paroxetine; SSRI safety debated, engage Psych/MFM), VTE (LMWH preferred), asthma, OUD (methadone & suboxone safe in pregnancy); avoid tobacco, EtOH, drugs; review medications and check for teratogens
- Infertility: evaluate after 12mo unprotected intercourse in <35yo, 6mo in ≥35, sooner if >40; fertility tx covered by insurance in MA
- Hx: prior OB/GYN hx (menstrual hx, pregnancies, PID, fibroids/polyps, abnl Pap, endometriosis, contraceptive use), sexual hx (timing, frequency, sexual dysfunction), hx chemo/XRT, meds, substance use, FHx. Ddx: see amenorrhea above
- Dx: ovarian reserve tests, pelvic/transvaginal U/S, PCOS w/u, STI & fallopian tube patency testing, TSH, PRL, **semen analysis**
- Tx: fertility awareness (intercourse qod cycle d9-14, or from 5d before and day of ovulation); refer to Repro-Endo for other w/u, induction of ovulation, IVF, or donor oocytes

Contraception (CDC USMEC 2016; CDC 2020 Summary; [a]Society of Fam Planning), resource for patients: bedsider.org

- 45% of pregnancies are unplanned → r/o pregnancy before initiating contraception → LARCs (IUD, implant) are most effective
- Hormonal methods (including LARC) take ~1w to take effect → always recommend backup method (condoms) for 7d

	Use	1y Failure Rate*	Pros/Cons	Contraindications (A: Abs, R: Rel)
Estrogen-progestin^				
Combined Pill	Daily	9% (0.3%)	Pros: ↓menses, PMS, cramps, acne, endometrial/ovarian CA Cons: n/v, breast tenderness, can ↑HTN/TGs, ↓libido, spotting, cannot start if <21d post partum)	**A**: Hx VTE, thrombogenic mutation; Breast or liver CA w/in 5y; Migraine w/ aura or >35yo & any migraine; >35yo & >15 cig/d; hx CVA; Uncontrolled HTN; DM w/ vascular dz, CAD, CVD,valvular dz, ESLD; R: Obesity (↓efficacy of some rings/patch)
Vaginal Ring	3w in, 1w out	9% (0.3%)		
Patch (e.g. Xulane, Ortho Evra)	Weekly x3w, 1w off; apply to arm, torso, or buttock	9% (0.3%)		
Progestin-only				
IUD (hormone content: Mirena/Liletta > Kyleena > Skyla)	M/L q8y Kyleena q5y Skyla q3y	0.2%	Pros: long-acting, lighter periods, may reduce cramping/anemia, discreet Cons: irregular bleeding, requires removal, physical complications (rare) Pt preference: amenorrhea (~18%)	**A** (all): active breast CA or w/in last 5y **A** (IUD): abnl uterine cavity; unexplained vag bld; active STI, PID, endometritis at insertion; endometrial or cervical CA **R** (all): APLAS, ESLD, liver CA, breast CA >5y ago **R** (implant): unexplained vag bld **R** (injection): unexplained vag bld, CV RF, ischemic heart disease, PVD, uncontrolled HTN, DM w/ end-organ damage, CVA **R** (pill): malabsorption
Implant (Nexplanon)	q3y to upper arm (q5y efficacy[a])	0.05%		
Injection (Depo-Provera)	q3mo IM/SQ to arm, thigh, or buttock	6% (0.2%)	Pros: long-acting, discreet Cons: irregular bleeding; temp ↓BMD; prolonged return to fertility (1y); may worsen HA, acne, mood	
Pill (e.g. Micronor, Slynd)	Daily	8% (0.3%)	Pros: no effect on breastfeeding Cons: irregular bleeding, HA, acne, mood sx, timingΣ	
Hormone-free				
Copper IUD (Paragard)	q10y (12-20y efficacy)	0.8% (0.6%)	Pros: long-acting, safe in ESLD Cons: heavier bleeding, cramping	**A**: Same as progestin IUDs above; copper allergy, Wilson's dz
Male condom	Every encounter	18% (2%)	Pros: STI prevention Cons: requires pt adherence	**R:** Oil-based lubricant w/ latex condom
Tubal Ligation Vasectomy	Permanent	0.5% 0.15%	Pros: available to men and women Cons: irreversible, surgical	**R**: Surgical risk **R**: Pt unsure of decision

* Typical use: % women who will have pregnancy in 1 year on this method (perfect use in parentheses); ΣNewer formulations like Slynd maintain efficacy with 24h missed window (Curr Obstet Gyn Rep 2022;11); ^Estrogen-progestin methods can be used continuously to avoid withdrawal bleed.

Oral Contraceptives (OCPs) (Quick Start Algorithm): start anytime (exclude preg + 7d backup method).

- **OCP selection**: estrogen (ethinyl estradiol) – 30-35mcg: less breakthrough bleeding. 20mcg: less estrogen SE. Progestin – 2gen (levonorgestrel, norgestrel): ↓VTE risk. 3gen (norgestimate, desogestrel): ↓androgenic SE, ↑VTE risk
- **Patient Resources**: Bedsider.org is a great resource for patients to explore options

Emergency Contraception (Obstet Gynecol 2015;126:e1; NEJM 2021;384(4); PCOI)

- **Plan B** (levonorgestrel 1.5mg x1 or 0.75mg q12h x2): OTC, use w/in 72h, less reliable if BMI >25. **EllaA** (ulipristal 30mg x1): requires Rx, use w/in 120h, less reliable if BMI >30. **Paragard/Mirena/Liletta**: place within 120h (Paragard okay up to 160h), most effective
- In cases of **sexual assault**: refer pt to ED for an exam by a trained SANE RN. If IPV: ask if partner has access to online medical records prior to detailed documentation and prepare safety plan. **MGH HAVEN referral: 617-724-0054**

OPTIONS COUNSELING (TEACH)

Options counseling is an opportunity for the pregnant person to consider, in conversation with a provider, whether to continue the pregnancy and parent the child, continue the pregnancy with a plan for adoption, or have an abortion. Particular attention to neutralizing language to avoid potential coercion is imperative. For people who desire abortion, see PCOI or abortionfinder.org for list of providers in MA. Avg cost ~$500, 50% pay out of pocket. Counseling: **1-866-4-EXHALE.**

Medical Abortion (MAB) (95-98% effective)

- Eligibility: ≤10 wks gestation, no ectopic risk (history alone or U/S if equivocal); **no** (1) IUD in place, (2) mifepristone or misoprostol allergy, (3) chronic adrenal failure/long-term corticosteroid use, (4) hemorrhagic disorders, on AC, symptomatic anemia, (5) porphyria
- Workup: serum or urine hCG test; **no routine pre-MAB lab testing needed if no underlying conditions; LMP can date pregnancy accurately & safely in most cases** (U/S NOT universally required); offer STI testing & immediate post-abortion contraception
- Protocol: PO mifepristone x1 → buccal or vaginal misoprostol in 24-48h → pt passes pregnancy at home over hrs. May experience cramping and bleeding. Tx with NSAIDs. F/u history and home urine pregnancy test OR serial bHCG testing OR U/S in 7-14d

Surgical Abortion (<24wks gestation, 99% effective): same-day office procedure → no f/u unless complications

Parenting: obstetrics

Adoption: resources for public and private agencies

POSTPARTUM CARE (ACOG Postpartum Toolkit, 2018)

Key Screening Items: proactive questions and anticipatory guidance about nl vs abnl mitigates complications and worry; **Screen for IPV.**

- Vaccines: all vaccines safe while breastfeeding except smallpox (give yellow fever and MenB only if benefits > risks); recommend all w/ baby contact receive flu & Tdap
- Contraception: can start progestin-only options (IUD, implant, injection, pills) immediately postpartum & estrogen-containing options 21-28d postpartum (42d if VTE risk factor).
- Breastfeeding: see Lactmed for restarting medications. Challenges: nipple pain (tx lanolin, breast shield), plugged ducts (aspiration if >72h), inadequate milk supply, mastitis (10% breastfeeding mothers; assoc w/ edema, erythema, ± fever/chills; if c/f infection, r/o abscess w/ exam (tx w/ I&D) and Rx dicloxacillin or keflex; encourage continued breastfeeding). Consider referral to lactation consultant. Remind mom federal law requires break time & dedicated space at work for lactation
- SUDs/Analgesia: postpartum period high risk for SUD/relapse. Methadone & buprenorphine safe w/ breastfeeding, should be continued (risk of relapse during postpartum). Screen for AUD. Encourage smoking cessation (pt & all household members). Acetaminophen and ibuprofen safe during breast feeding; avoid NSAIDs if HTN. Butorphanol, morphine, hydromorphone are preferred opioids if needed
- Common sx (often self-resolve): vaginal soreness & discharge, constipation, hemorrhoids, cramps, breast engorgement, urinary/fecal incontinence, hair loss (w/in 5mo), mood swings ("baby blues")
- Persistent vaginal bleeding: normal to have small amount of red-tinged discharge for 1-2w PP (w/ red, heavy discharge for 1-2d); if soaking through pad/tampon in <1h ± pain, fever, tenderness, may be signs of infection, refer to ED
- Perineal pain, dyspareunia, and sexual dysfunction: >10% report pain 1y post-vaginal delivery (RF = 3rd/4th degree tears, operative delivery, vaginal atrophy while breastfeeding). Tx: water-based lubricants, topical estrogen, pelvic floor therapy, scar tissue ablation. Decreased libido common and normal (50% at 3mo, 30% at 6mo)
- Postpartum depression: w/in 12mo after birth; incidence of 11-20%; screen with PHQ9, Postpartum Depression Scale, or Edinburgh Postnatal Depression Scale; tx with peer counseling, CBT, SSRI.

Pregnancy-Related Complications of Cardiovascular Disease and Endocrinopathies

- Postpartum period high risk for: flares of underlying autoimmune disease, peripartum cardiomyopathy
- Excessive gestational weight gain, obesity, preterm birth (<32w) ↑risk for CVD in mom; screen annually for modifiable RF

	Future Risk	Postpartum Screening	Risk Mitigation
Gestational Diabetes/ Diabetes	- ↑risk of recurrent GDM, pre-DM, T1DM, T2DM (7x higher), CVD, & metabolic syndrome (esp. w/in 5y) - Uncontrolled DM ↑risk birth defects	- 75g OGTT or fasting BG at 4-12w postpartum (Diab Care 2021;44:S15). If ⊕, screen q1y. If ⊖, q3y for life - If T1DM, TFTs x1 (if never done)	- Encourage breastfeeding - If overt DM: target A1c 6-6.5, consider ASA 81mg qd in future pregnancies to ↓pre-eclampsia risk
Pre-Eclampsia/ HTN	- ↑risk of stroke 48h-10d postpartum - ↑risk of CKD in first 5y - ↑risk of ASCVD (JACC 2019;74:1376)	- Close BP monitoring up to 6w PP - BP >140/90 warrants eval - Repeat UACR/UPCR to quantify baseline proteinuria, CBC for plt, CMP for LFTs and creatinine	- Encourage breastfeeding - Early goal BP <160/100, later <120/80 - Add pre-eclampsia as ASCVD risk-enhancer - **Consider ASA 81mg qd in future pregnancies to ↓pre-eclampsia risk**

Benign Prostatic Hyperplasia (BPH)/Lower Urinary Tract Sx (LUTS) (J Urol 2021;206:806; PCOI)

- Sx: increased urinary frequency, urge, difficulty initiating or weak stream, small amount of urine w/each void, leaking or dribbling, and/or sensation of incomplete void. Present in >50% of men over 60 y.o. w/increased incidence with older age (~90% >85 y.o.)
- DDx: urethral stricture, bladder neck contracture, prostate ca, bladder ca, bladder calculi, UTI, prostatitis, neurogenic bladder
- Eval: HPI, sexual hx, assess sx burden via International Prostatism Symptom Score (IPSS), perform a PE (DRE), obtain UA (blood, bacteria, glucose, protein), 24-hr voiding diary, and consider PVR and/or urodynamic testing prior to Rx initiation;
- Possible Complications: urinary retention, persistent gross hematuria, bladder stones, recurrent UTI, hydronephrosis, renal failure
- Screening: BPH/LUTS don't appear to be RFs for prostate Ca; important to counsel pts & have shared decision-making re: PSA screening annually vs q2yrs at ages 55-69 given high degree of false positives (~70%) and risks/benefits of side effects vs medical Rx
- Rx: if sx worsening despite initial watchful waiting & behavior changes (avoid alcohol/caffeine, limit PM fluid intake, avoid antihistamines/decongestants/allergy meds which can worsen sxs), may consider medical therapies including:
    - **Alpha-blockers** (terazosin, doxazosin, tamsulosin, alfuzosin, silodosin): **initial** therapy; MOA - relax muscles near the prostate, max efficacy in 1 month; ADEs: headaches, hypotension, dizziness, or feeling lightheaded or tired.
    - **5-alpha reductase inhibitors** (finasteride or dutasteride): MOA - inhibit testosterone to shrink prostate, max efficacy in 6-12 months; ADEs: decreased libido, problems with erection or ejaculation.
    - **PDE-5 inhibitors** (tadalafil): preferred for men with ED, max efficacy by 4 weeks ADEs: headache and back pain.
    - **Combination Rx (alpha blocker + 5-alpha reductase inhibitor):** consider addition of 5ARI if prostate >30cc, Rx combo may be more effective for sx reduction & decreasing risk of overall BPH progression than either agent alone
    - **Saw Palmetto (plant extract)**: limited data to support efficacy over placebo but anecdotally may help improve sxs
- Procedures: **Transurethral resection of prostate (TURP)**: Most common procedural intervention – involves insertion of thin tube into urethra & cutting away pieces of prostate causing blockage (often does not require total prostatectomy). Additional minimally invasive procedures include transurethral needle ablation (**TUNA**) & transurethral microwave thermotherapy (**TUMT**).

  Potential complications: reverse flow of semen (empties into bladder & not out of penis) – does not affect ability to orgasm but can affect fertility; less common side effects: urinary incontinence, inability to initiate or sustain erection.

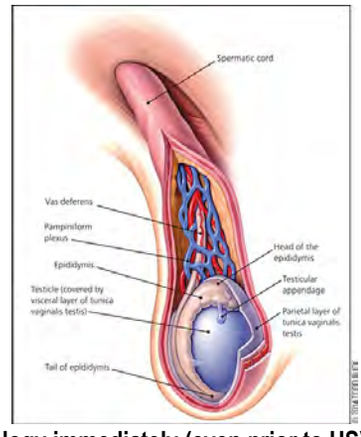
Erectile Dysfunction (J UROL2018;200:633; PCOI)

- Sxs: inability to consistently attain or maintain erections rigid enough or of sufficient quality for sexual intercourse. Affects ~22% of men 60-69 and 30% of men >69.
- DDx: distinguish from decreased libido 2/2 testosterone deficiency (see *Endocrine section*), MDD, use of prescription/illicit drugs; ejaculatory dysfunction (ex: premature or retrograde ejaculation); anatomic anomalies (ex: Peyronie's Dz)
- RFs: CVD/PAD, CKD, HLD, HTN, obesity, smoking, sleep disorders (OSA, RLS), hyperglycemia, DM; should additionally perform complete medication review as many commonly prescribed meds can cause ED (PCOI, Table 2)
- Rx: First line - lifestyle modifications for pts with above RFs (ex: tobacco cessation, EtOH reduction), may consider Pharm Rx:
  All PDE5 inhibitors are contraindicated in pts on nitrates. Co-admin of tamsulosin is less likely to cause hypotension than doxazosin

Medication	Dosing	Side Effects
Sildenafil (Viagra)	• Start: 50 mg, dose range 25-100 mg prn according to side effects. • Take 1 hour prior to sex on empty stomach, effective for 4 hours.	Rarely can cause blue-tinged vision.
Vardenafil (Levitra)	• Start: 10 mg, dose range 2.5-20 mg. • Take 1 hour prior to sex, effective for 4 hours. Taking with fatty meals may cause reduced efficacy.	Can cause QTc prolongation (avoid in congenital QT prolongation or with additional QTc prolonging meds)
Tadalafil (Cialis)	• Start: 10 mg, dose range 5-20 mg. • Take 30 minutes prior to sex, peaks at 2 hours, effective for 24-36 hours.	More tolerable than other PDE-5 inhibitors with alpha-blocker tamsulosin 0.4 mg. Myalgias in 15% of users.
Avanafil (Stendra)	• Start: 100 mg, dose range 50-200 mg. • Take 15-30 minutes prior to sex with or without food.	Fastest onset. Limited side-effect profile.

When to refer: urology referral for adolescents/young adult w/primary ED (never been able to achieve erection); failure of initial first-line oral Rx; contraindications to PDE-5 inhibitor Rx; other specialized testing warranted (ex: penile vascular test, nocturnal penile tumescence)

Scrotal/Testicular Masses (Am Fam Physician 2014; 89:723)



- Scrotal masses = common presentation in primary care – scrotal pain ~1% of all ED visits.
- Normal PE: firm but not hard testes, nearly equal in size, smooth/ovoid, normal testicle length ~4-5 cm after puberty, epididymis is posterolateral to testicle, vas deferens exits via tail of epididymis and joins vascular pedicle of testicle to form spermatic cord.
- DDx: helpful to begin assessment by distinguishing **painful vs painless**:
- Painful: torsion (acute, N/V, abnormal cremasteric reflex, blue dot sign, CRP<24) vs epididymitis/orchitis (most common, +/- fever & dysuria, erythema, CRP>24) vs hematocele/testicular rupture (rare, associated with trauma)
- Mixed pain/painless: testicular cancer (ages: 15-34, firm unilateral nodule, hx of cryptorchidism in childhood or Klinefelter synd.; obtain α-fetoprotein [AFP], ß-HCG, LDH) vs hernia (painful w/strangulation; test via Valsalva maneuver)
- Painless: hydrocele (transillumination w/pen light) vs varicocele ("bag of worms" feel in 15% of males affected, typically occurs in adolescence)

Imaging/labs: Scrotal U/S is best for distinguishing above ddx coupled with inflammatory vs markers as above if there is a high index of suspicion. **If c/f torsion, surg emergency. Consult urology immediately (even prior to US).**

Joshua Ellis

INSOMNIA (PCOI)

35-50% of population; chronic insomnia **>3mo**. difficulty initiating or maintaining sleep and compromised daytime function (UTD)

- Hx: evaluate chronicity, stressors, effect on fxn/mood, # awakenings and triggers, sleep hygiene; meds, PMH, sleep log for 1w
- Ddx: **Medical:** r/o pain, primary medical condition (e.g., PSYCH: PTSD, mood d/o; PULM: COPD, asthma; CV: CHF; GI: GERD; GU: nocturia), SUDs, medications (e.g., stimulants, steroids, BBs, SSRIs, SNRIs, OCPs, chronic opioids)
  - **Primary sleep d/o**: insufficient sleep syndrome (<7-8h allotted to sleep), psychophysiologic (inability to sleep due to stress or anxiety about sleep), paradoxical (no e/o sleep d/o), RLS, Periodic Limb Movements of Sleep (PLMS), OSA, idiopathic (starting in childhood), circadian rhythm disorder (delayed sleep phase; advanced sleep phase-common elderly)
- Rx: **Sleep hygiene**: regular sleep schedule 7d/wk, exercise, if lying in bed awake get up till sleepy, ~~no~~ reduce/eliminate caffeine/EtOH/nicotine, quiet/dark BR, eliminate bright lights/screens in pm; **CBT-I** (**first line** with strong evidence, hard to access), (J Clin Sleep Med 2021;2,263). **Meds:** scant evidence on safety/efficacy but often tried: low dose melatonin, trazodone (UTD); **(WEAK evidence)**: sleep maintenance (doxepin), sleep onset (ramelteon, triazolam), both (DORA, eszopiclone, zolpidem, zaleplon, temazepam). Goal is Rx hypnotics for <4w only and careful risk/benefit for BZRA agents (J Clin Sleep Med 2017;13:307); treat mental health disorders

SLEEP APNEA (JAMA 2020;14:389, PCOI)

Obstructive (upper airway occlusion) and/or central (↓resp drive). OSA affects ~10% of adults

- Presentation: daytime somnolence (use Epworth Sleepiness Scale), morning HA, witnessed apnea/gasping, snoring (Sn > Sp), depression, nocturia, pHTN; RF: obesity, anatomy, incr age, ♂, post-menopausal, EtOH, FHx, CHF. Screen for OSA w/ STOP-BANG (≥3 symptoms with Sn 90%) (JAMA 2021; epub)
- Dx: **sleep study in-lab** (polysomnography (PSG); gold standard) vs **at home** (cannot detect other sleep d/o or central apnea, often req by insurance over PSG; home sleep study underestimates the degree of sleep apnea); both quantify apnea-hypopnea index (AHI) = sum of events/h (mild 5-15, mod 16-30, severe >30), minimum O_2 saturation, and percent of time below 90%. Apnea/nocturnal O_2 requirement often observed inpatients, but can confirm diagnosis o/p only.
- Tx: **behavioral**: weight loss, avoid ETOH/sedatives, position (avoid supine sleep, elevate HOB); **Positive Airway Pressure**: CPAP, BiPAP, ASV (for central, risky in CHF), APAP (most common, auto adjusts PAP); **other:** oral appliance (dentist referral), surgery, modafinil (for daytime sleepiness refractory to CPAP). Managed by PCP (HST then APAP), Sleep ENT (PAP, surgery, HGNS), Sleep Neurology (PAP, meds), or Pulmonary (pHTN). Important to identify preoperatively (JAMA 2019;321;18:1788).

OBESITY HYPOVENTILATION SYNDROME

- Presentation: **awake** alveolar hypoventilation not attributed to other conditions (**dx of exclusion**: r/o alt etiologies of hypercapnia and hypoventilation), in an obese individual (AJRCCM 2019;200;3:e6)
  - RF: obesity (BMI>30) esp severe (BMI≥40, Class III), central obesity, severe OSA
- DDx: COPD, ILD, neuromuscular disorders, chest wall disorders, hypothyroidism, chronic sedative use
- Dx: VBG CO2>27, PaCO2>45, PaO2<70; also BMP (r/o lyte disorder), CBC (polycythemia may be associated, monitor response to rx), TSH, PFTs (to exclude other causes – nml does not exclude OHS), CXR, PSG (identify sleep d/o breathing, gold standard)
- Tx: BiPAP and weight loss/bariatric surgery. Assess for complications (pHTN, HTN, CHF, insulin resistance)

RESTLESS LEG SYNDROME (RLS) (PCOI)

- Presentation: *URGE*: Urge to move legs, Rest induces symptoms, Getting active brings relief, Evening worsens sxs.
- Common triggers: caffeine, nicotine, ETOH, dopamine antag, most antidepressants, antihistamines
- Assoc conditions: iron deficiency (and work up of etiology), CKD, pregnancy, tremor, Parkinson's, MS, movement disorders, OSA
- Dx: Clinical (PSG if unsure, PLMD), Fe/TIBC/Ferritin/CBC, BMP (CKD); DDx: MS, akathisia, myalgia, PMR/myositis, neuropathy, stasis/edema, PVD, arthritis, nocturnal leg cramps, positional discomfort, habitual foot tapping
- Tx: stop trigger meds, avoid EtOH/nicotine, treat OSA, iron supplement to ferritin >75; DA agonists (take 1-1.5h before trigger or qhs) - pramipexole, ropinirole, carbidopa/levodopa (<3x/w, high risk rebound), rotigotine patch; a-2-d Ca channel ligand: pregabalin, gabapentin; comorbidities may guide Rx; refer to neurology if refractory to monotherapy.

OTHER SLEEP DISORDER

Narcolepsy: chronic daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis (1/3 pts have all three symptoms so consider narcolepsy even if only chronic daytime sleepiness) (NEJM 2015;373:2654); Dx: PSG (exclude alternative causes) and Multiple Sleep Latency Test (MSLT). Tx: Requires specialty management. Basics of treatment include good sleep hygiene and trigger avoidance (BZD, Opiates, Antipsychotics, EtOH, Caffeine, Alpha1Antag).

Parasomnias: complex movements and behaviors during sleep. Associated with NREM (sleepwalking, confusional arousal, sleep terrors, sleep related eating disorder) and associated with REM (nightmare disorder, REM sleep behavior disorder) (AJM 2019; 132:292).Dx: Mayo Sleep Behavior Questionnaire can help dx, obtain video PSG if uncertain and consider MRI. Tx: is to improve sleep hygiene (EtOH, stress, sleep deprivation, Rx OSAS) and assess safety. Melatonin 3-18mg is first line rx.

CHRONIC COUGH (AFP 2017;96:575; NEJM 2016;375:1544)

- Time course: acute (≤3w) vs. subacute (3-8w) vs. chronic (>8w)
- Common causes: upper airway cough syndrome (UACS), asthma, GERD; these three account for 90% (18-62% pts have combo)
- General approach:
  1) History (smoking, URI, ACEi use, GERD sx); remove possible offending agent
  2) Consider CXR if cough >8 weeks, especially if ↓suspicion for UACS/asthma/GERD
  3) Start empiric tx for UACS/asthma/GERD sequentially until resolution → tx should be *added* to initial regimen
  4) Consider PFTs, esophageal pH monitoring, chest CT, sputum tests, cardiac studies if sx persist despite treatment of usual causes

Etiology	Characteristics	Treatment
Upper Airway Cough Syndrome (UACS)	Formerly *post-nasal drip syndrome*. Most common cause of subacute/chronic cough. Cough may be only sx. Exam: throat/nose may reveal cobblestoning. Common causes: allergic/non-allergic rhinitis, sinusitis	Avoid environmental triggers of allergic rhinitis. Steroid or antihistamine nasal spray, oral antihistamine/ decongestants, and saline nasal rinse for symptom relief. Improve in wks- 2 mos
Asthma	Typically p/w episodic wheezing & dyspnea. Cough variant asthma p/w only cough. Pt may have h/o atopy. Exam: ± nasal polyps. Need spirometry w/ bronchodilator response & bronchoprovocation (methacholine challenge) for dx	PRN bronchodilators ± inhaled corticosteroids. Some pts may use only seasonally. See *Asthma* for stepwise therapy
GERD	30-40% of chronic cough. Epigastric burning sensation, sour taste in mouth (although sx absent in >40% of patients)	Lifestyle modifications, moderate dose PPI/H2 blocker. Consider *H. pylori* testing
Respiratory tract infection	H/o recent viral illness. 2/2 postnasal drip/UACS or direct effect of virus on bronchial reactivity/cough receptors. Pts have been shown to experience transient bronchial hyperreactivity as well	UACS tx as above. 2nd gen (cetirizine) or 3rd gen (fexofenadine) antihistamine. If bronchial hyperreactivity, tx w/ usual asthma care
ACE Inhibitor	Produces cough in 3-20% of pts. 2/2 ACEi-mediated increase in bradykinin. Sx can occur 1w to 6mo after starting	Withdraw ACEi (resolves within 1-4w), change to ARB (**not** associated with cough)

Other causes: post-infxn (self-limited; can last 3+ months, treat sx), COPD, OSA, non-asthmatic eosinophilic bronchitis, chemical irritant (e.g., cigarette smoke), laryngopharyngeal bronchitis, psychogenic/habitual cough, bronchiectasis, CA, TB, sarcoid

RHINOSINUSITIS (Otolaryngol Head Neck Surg 2015;152:598; NEJM 2016;375:962; Clin Infect Dis. 2012; 54(8):e72)

- Time course: acute (<1mo) vs. subacute (1-3mo) vs. chronic (>3mo); recurrent (4 or more annual episodes)
- Dx: rhinorrhea (viral=clear, bact=purulent) + nasal obstruction or facial pressure/pain/fullness. A/w anosmia, ear fullness, cough, HA
- Acute rhinosinusitis is *infectious* while chronic is *inflammatory* (atopy, asthma, granulomatous disease, immunodeficiency, CF)

Etiology	Time Frame	Treatment	
Viral: most common cause	7-10d	Symptom control, oral decongestant	• NSAIDs/Tylenol for pain • Saline irrigation/Netipot • Topical nasal steroids, decongestant, expectorants
Bacterial: only 0.5-2% of acute rhinosinusitis. *S. pneumo* (41%), *H.flu* (35%)	>10d, or worsening w/in 10d after initial improvement	Watchful waiting in pts w/ follow-up vs. amox-clav 875mg BID** or doxy 100mg BID x5-7d	
Fungal: mucor (invasive) in DM, immunocompromised	Acute (invasive) to more chronic (>3mo)	Surgical removal of fungal mucin or "fungal ball" (mycetoma). ENT emergency if invasive (destruction of sinus, erosion into orbit or brain)	

** Higher dose Augmentin (2g BID or 90 mg/kg/d BID) in pts w/ RFs for resistance: regional resistance pattern, age 65+, hospitalized in last 5d, abx use in last month, immunocompromised, DM/cardiac/renal/hepatic disease, severe infxn (fever >102F, suppurative complication)

- Chronic rhinosinusitis: confirm diagnosis w/ CT or endoscopy; treatment varies by presence or absence of nasal polyps
  - No polyps → trial saline irrigation/intranasal steroid
  - ⊕ polyps → add short course of PO steroid ± ASA desensitization if concern for ASA-exacerbated respiratory disease
- Complications: meningitis, periorbital/orbital cellulitis (pain, edema, proptosis, painful eye movement, diplopia), subperiosteal/intracranial/epidural abscess, osteomyelitis of the sinus bones, septic cavernous sinus thrombosis
- Alarm symptoms: persistent fevers >102F; periorbital edema, inflammation, or erythema; CN palsies; abnormal extraocular movements; proptosis; vision changes (diplopia, impaired vision); severe HA; AMS; meningeal signs

PHARYNGITIS (JAMA 2012;308:1307; NEJM 2011;364:648; CID 2012;55:e86)

- **Usually viral** (suspect if +conjunctivitis, coryza, cough, diarrhea, hoarseness, discrete ulcerative stomatitis, viral exanthema)
  - Only 5-15% of adult sore throat visits are Group A Strep (GAS)
- **Exclude dangerous etiologies**: epiglottitis, peritonsillar abscesses, infxn in submandibular or retropharyngeal space, acute HIV
- **Identify & treat GAS** to ↓risk of suppurative complications (peritonsillar abscess, cervical lymphadenitis, mastoiditis), prevent rheumatic fever (lower risk in adults), ↓transmission, & improve sx. ASO titers useful only in dx of non-suppurative sequelae of GAS
  - Centor Criteria: 1 point for each - tonsillar exudates, tender ant. cervical LAD, fever, ∅ cough; (-1pt if age ≥45)
    - 0-2: no testing, treat sx. 3-4: send Rapid Strep antigen detection test (Sn 70-90%, Sp 95%) ± throat Cx (if neg rapid but ↑clinical suspicion; not indicated for routine use in adults w/ neg rapid)
  - Tx: PO penicillin V 500mg BID x10d; amoxicillin 500mg BID x10d; IM benzathine penicillin G 1.2milliU x1
    - PCN-allergic: cephalexin 500mg BID x10d
    - β-lactam sensitivity: clindamycin 300mg TID x10d; azithromycin 500mg QD x1d, then 250mg QD x4d
- Symptomatic tx: OTC lozenges (e.g. Sucrets, Cepacol), throat sprays, NSAIDs/Tylenol for pain relief. No PO steroids
- Follow up: if no improvement in sx in 5-7 days, evaluate for other infectious causes (e.g., mono, HIV, GC/chlamydia) or suppurative complications such as tonsillopharyngeal cellulitis, abscess, or acute otitis media

EYE

General Evaluation: see *Ophthalmology*

- Initial eye exam: visual acuity (Snellen chart, w/ glasses if worn), pupils (reactivity, APD), confrontational visual fields, EOM, intraocular pressure (palpate for firmness), color vision (Ishihara cards)
- **Red Flags (urgent ophtho eval):** severe pain, HA/nausea, photophobia, severely decreased vision, abnormal pupil exam, corneal opacities, chemical injury, recent eye surgery or trauma, double vision, new onset flashes or floaters

Vision Loss

- Acute, Painless (ED): GCA; non-arteritic ischemic optic neuropathy (~60y, +APD); central retinal artery occlusion (vasculopathy, +APD, ± amaurosis fugax); central retinal vein occlusion (DM, HTN, hypercoag, glaucoma, OCPs, hyperviscosity, ± RAPD); vitreous hemorrhage (DM, retinal detachment/tear); retinal detachment (flashes of light, floaters, ± abnl red reflex); pseudosudden vision loss (gradual monocular loss misperceived as sudden if other eye occluded)
- Acute, Painful (ophtho w/in 24h): optic neuritis (unilateral, <50y, blurry vision, flashes of light, +APD, pain worse w/ eye movt); acute closed-angle glaucoma (deep brow ache, ± n/v, halos around lights)
- Gradual, Painless (routine referral): refractive error, cataracts (glare, halos, trouble night driving), open-angle glaucoma (RF: age, FHx, AA/Hispanic), diabetic retinopathy (c/b macular edema, vitreous hemorrhage, macular ischemia, tractional retinal detachment), age-related macular degeneration (central, RF: tobacco, poor diet, age, FHx), meds, idiopathic intracranial HTN (RF: ♀, obesity, steroids, OCPs, high-dose VitA, tetracyclines), mild amblyopia

Red Eye (AFP 2010;81:137) for tx see *Ophthalmology*

- Painless: subconjunctival hemorrhage (unilateral, no vision Δ), episcleritis (painless w/o vision Δ or discharge, unilateral focal erythema, self-limited), dry eye syndrome (b/l itching, burning, photophobia, foreign body sensation, diffuse hyperemia), blepharitis/Meibomian gland dysfunction (b/l lid margin burning, itching, AM crusting)
- Painful: conjunctivitis (itching, burning, FB sensation), keratitis (photophobia, tearing, hyperemia; 2/2 corneal ulcer or VZV/HSV), severe tear deficiency (Sjogren's, GVHD), iritis/uveitis (unilateral, photophobia, tearing, sluggish pupils; autoimmune), scleritis (HA, boggy red/pink sclera, tender globe, pain with EOM, no vision Δ), endophthalmitis (floaters, vision Δ, fixed dilated pupil, hypopyon; c/f fungemia), acute angle closure glaucoma (unilateral, HA, halos, n/v, vision Δ, fixed dilated pupil, globe firmness)
- Swollen eyelid (AFP 2015;92:106): hordeolum = stye (tender nodule 2/2 occluded Meibomian gland), chalazion (painless nodule 2/2 chronic granulomas), contact dermatitis (caution w/ topical steroids), preseptal or orbital cellulitis (see *Orbital and Preseptal Cellulitis*)

Conjunctivitis (JAMA 2013;310:1721):

- Viral > bacterial. Very contagious: strict hand hygiene, avoid contacts until sx resolves
- Dx: PCR, GS, or Cx rarely needed – consider if severe purulence, refractory to tx, recurrent, immunocompromised, or c/f GC/CT
- Avoid contact lenses, topical corticosteroids, OTC vasoconstrictors (rebound hyperemia)

Etiology	Presentation	Dx	Tx
Viral (most common)	History: sick contact, URI sx, watery d/c, gritty sensation, itching. Exam: intense hyperemia, ± periocular swelling, preauricular LAD	Typically adenovirus	Cool compresses, artificial tears. If c/f HSV/VZV: topical/PO tx + ophtho
Bacterial	History: mucopurulent d/c, pain/stinging. Exam: crusting, intense hyperemia, LAD rare	Typically *S. pneumo, S. aureus,* or *H. flu;* consider GC/CT if RF	Erythromycin ointment 0.5% QID x7d (mild) or Polytrim 1-2 drops QID x7d (mod-severe, ↓ time to recovery). GC: PO abx + ophtho
Allergic	History: intense itching, painless tearing, hx atopy, allergic rhinitis. Exam: **bilateral**, mild hyperemia	Chronic or seasonal	Avoid allergens. Cool compresses, artificial tears. OTC anti-histamine/mast-cell stabilizer drops (e.g., ketotifen BID) ± PO anti-H1

EAR (AFP 2018;97:20)

Ear Pain

- Primary (otitis externa/media, foreign body, Eustachian tube dysfunction, barotrauma, cellulitis, cholesteatoma, mastoiditis, Ramsay Hunt Syndrome 2/2 VZV) vs Secondary (TMJ, Bell's Palsy, sinusitis, dental work, GERD, tumor, GCA, MI, thoracic aneurysm)
- **Red Flags**: signs of malignant otitis externa (HA/pain out of proportion to exam, fever, immunosuppressed, granulation tissue in floor of ear canal) or otitis media spread (mastoid pain/swelling, bloody otorrhea, facial weakness, vertigo, nystagmus, photophobia)

Etiology	Presentation	Dx	Tx
Otitis Externa	History: otalgia, itching. DM, water exposure, cerumen. Exam: tragus/pinna pain, ear canal edema/erythema, ± otorrhea/LAD/TM perf	Typically *PsA* or *S. aureus*. Assess for other skin conditions	Depends on if TM is intact and severity. Topical: acetic acid, steroid, abx (FQ) oto-drops (UTD algorithm)
Otitis Media	History: recent URI, smoking, hx Eustachian tube dysfunction. Exam: TM bulging ± immobile w/ erythema, conductive hearing loss	Viral > bacterial (*S. pneumo, H. flu, M. catarrhalis)*	If mild-mod, consider Rx if no improvement at 2-3d. Amox-clav BID x5-10d (or amox 500 TID). ENT if ruptured TM does not close in 6w

Tinnitus: false perception of sound in the absence of acoustic stimulus (NEJM 2018;378:1224; AFP 2014;89:106)

- History: dizziness/vertigo (consider Meniere's), hearing loss, laterality (c/f schwannoma), meds (ASA, loops, abx), trauma, CVA, HA, depression/anxiety. Red flags: persistent + pulsatile, unilateral + hearing loss, vertigo, focal neuro deficits – consider audiology referral, imaging w/ CTA or MRA/MRV
- Tx: r/o underlying etiology. 20-50% have resolution spontaneously. If bothersome: CBT, sound therapy, tinnitus retraining therapy

Hearing Loss: RF - age, ♂, Caucasian, HTN, DM, CKD, immunosuppressed

- Conductive (mechanical): cerumen impaction, otitis externa/media, otosclerosis, ruptured TM, cholesteatoma (middle ear cyst)
- Sensorineural (neuro): presbycusis (age-related, gradual, symmetric, high frequency), noise-induced, Meniere's (asymmetric, +tinnitus, +vertigo), sudden sensorineural (acute, asymmetric, +tinnitus, **urgent eval**), barotrauma, tumor, meds, infxn

Primary Care Nodules

ADRENAL NODULES (>1CM) (Endocr Rev 2020;41:775; PCOI)

- Q: Is it malignant? (<5% 1° carcinoma, <2.5% mets): high-risk imaging findings: diameter >4 cm (93% Sn for adrenocortical CA), >10 HU on CT, heterogeneous, hypervascularity, irregular shape, calcification, ↑T2 signal on MRI, delayed contrast washout
- Q: Is it functionally active? (10-15%): exam & lab testing for all nodules >1cm (unless obvious myelolipoma) to r/o pheo & Cushing's syndrome (see table). Also test for hyperaldo if HTN, hypokalemia. Only test for production of excess sex hormones if clinical stigmata. **AVOID** testing inpatients due to high false ⊕ rates

Diagnosis	Suggestive Clinical Features	Laboratory Tests
Cushing's syndrome (~6-10%)	• HTN, metabolic syndrome, CVD, central obesity, prox muscle weakness, facial plethora • Glucose intolerance, DM • Decreased, normal, or increased bone formation	Baseline DHEAS. 1mg o/n dex suppression test (DST): if ⊕ send 24h urine free cortisol, then confirmatory 8mg o/n DST
Pheochromocytoma (~3-5%)	• HTN (5-15% don't have), palpitations, HA, diaphoresis, tremors • ≥10 HU on unenhanced CT, vascularity, cystic/hemorrhagic changes • Cardiomyopathy • "Pheo crisis": HTN/HoTN, psych d/o, multiorgan failure, hyperthermia	Plasma free (after 30m supine) or 24h urine fractionated metanephrines & catecholamines (Sn 98%, Sp 98%) **Do not perform DST (above) if concerned for pheo**
Hyperaldosteronism (~1%)	• HTN, hypokalemia • ↑risk stroke, CAD, afib, HF • ↑mortality (compared to matched population with essential HTN)	Plasma aldo & renin activity (correct hypoK and d/c aldo antagonists before testing). May need adrenal venous sampling
Hyperandrogenism	• ♀: virilization, hirsutism, acne, irregular periods • ♂: decreased libido, testicular atrophy, gynecomastia	DHEAS, total testosterone, 17-OHP

- Consider adrenalectomy: if ↑risk characteristics, >4cm, malignant, or hormonally active; surgery after hormonal eval
- Consider FNA: cannot distinguish between benign cortical mass & 1° adrenal CA. Useful if c/f adrenal met from another primary without known metastatic disease (**only** after excluding pheo)
- Follow up: repeat CT in 12mo. Consider annual DHEAS/1mg DST x4-5y (unknown effectiveness, guidelines do not recommend). Adrenalectomy if nodule grows >1 cm in 1 year, reaches 4cm, or becomes functional

THYROID NODULES (Thyroid 2016;26:1; Endocr Pract 2016;22:622; PCOI)

- Q: Is it malignant? ↑risk: h/o irradiation to head/neck, +family hx, h/o thyroid cancer syndromes (i.e., MEN 2), age <30

Workup: Thyroid Ultrasound, TSH

TSH normal or high	TSH low	
↓	↓	
r/o hypothyroid (FT4/TPO Ab)	FT4/T3, Thyroid radionuclide (^{123}I) scan	
↓	↓	↓
	"Cold nodule"	"Hot nodule"
↓	↓	↓
U/S-guided FNA if criteria met		Consider tx for hyperthyroidism if sx

- FNA: any nodule w/ extrathyroidal extension, extrusion through rim calcs, abnormal cervical LNs, adjacent to laryngeal nerve/trachea OR >1cm + solid/hypoechoic w/ irregular margins, microcalcs, rim calc, or taller than wide shape. No FNA for pure cystic nodules. ACR uses TIRADS
- Follow up (benign): based on U/S characteristics. If highly suspicious U/S findings, repeat US & FNA w/in 6-12mo. If low-moderate suspicious U/S findings, repeat U/S 12-24mo, consider FNA if >1-2cm change. Stop f/u after 2 neg FNAs

INCIDENTAL PULMONARY NODULES (<3CM) (Radiology 2017;284:228; Chest 2013;143:e93S; Thorax 2015;70 Suppl 2:ii1)

*NB: these guidelines are for **incidental findings** (see Fleischner Society Guidelines); recommendations for f/u of nodules found on LDCT for lung cancer screening are different as that population is high risk (see Lung-RADS classification)*

- Ddx: malignant (primary, met, carcinoid) or benign (majority; infectious granuloma, hamartoma, AVM, inflammatory)
- Is it malignant? *Pt characteristics*: ↑risk w/ h/o smoking, emphysema, pulmonary fibrosis, extra-thoracic cancer, asbestos exposure, age. *Nodule characteristics:* density (part-solid/ground glass>solid), larger size, faster rate of growth (increase >2mm on repeat CT), borders (irregular/spiculated>smooth), location (upper>lower lobe)
- Is it benign? demonstrates fat (pulmonary hamartoma) or characteristic calcification pattern (granuloma, hamartoma) or stability on CT for a defined period (>2y for solid and >5y for subsolid nodules)
- Follow-up: tailored to patient and type of nodule. *Subsolid* (entirely ground glass): if <6 mm, no routine f/u. If >6 mm, CT at 6-12mo, then CT every 2y until 5y. *Part solid*: if <6mm, no routine f/u. If >6 mm, CT at 3-6mo, then annual CT for 5y if unchanged and solid component <6 mm. *Solid nodules*: see below
- At MGH, consider referral to the Pulmonary Nodule Clinic: refer in Epic or call x38728 for appointment

Nodule type	< 6 mm	6-8 mm	> 8 mm
Single solid nodule			
Low risk	No routine follow up	CT at 6-12mo, then cons. CT at 18-24mo	Cons. CT at 3mo, PET/CT, or tissue sampling
High risk	Optional CT at 12mo	CT at 6-12mo, then CT at 18-24mo	Cons. CT at 3mo, PET/CT, or tissue sampling
Multiple solid nodules			
Low risk	No routine follow up	CT at 3-6mo, then cons. CT at 18-24mo	CT at 3-6mo, then consider CT at 18-24mo
High risk	Optional CT at 12mo	CT at 3-6mo, then at 18-24mo	CT at 3-6mo, then at 18-24mo

KNEE PAIN (PCOI)

- History: trauma, acute vs chronic, association with activity, constitutional sx, swelling, stiffness, instability, popping, locking or catching sensation, sensory/motor changes, BMI, orthopedic or rheumatologic hx. Have pt **point to area of pain** with one finger

Knee Exam		
Test	**Maneuver**	**Positive in**
Lachman (sim. to anterior drawer)	Pt supine with knee flexed to 20-30°. One hand on pt's femur, just above knee. Other hand on pt's tibia. Apply anterior pressure. If tibia feels less restrained, ⊕ test	**ACL** injury
Posterior Drawer	Pt supine with knee flexed, can stabilize foot by sitting on it. Place hands around tibia, apply posterior pressure parallel to femur. If less restrained motion, ⊕ test	**PCL** injury
McMurray	One hand over medial joint line with knee fully flexed. Externally rotate foot/tibia, apply valgus stress, and gently flex/extend knee. If clicking or pain at around medial joint line, ⊕ test	**Meniscal** injury

Location	Traumatic	Related to Activity	Atraumatic
Anterior	Quadriceps or patellar injury	**Patellofemoral syndrome***, Osgood-Schlatter, bursitis, quadriceps/patellar tendinopathy	RA, gout, pseudogout, septic joint
Lateral	Lateral meniscal tear, LCL injury	Iliotibial band syndrome	Lateral OA
Medial	Medial meniscal tear, MCL injury, tibial plateau fracture	Anserine bursitis	Medial OA, saphenous nerve entrapment
Popliteal	PCL injury	Popliteal artery entrapment, Baker cyst	Popliteal artery aneurysm, DVT

*Most common etiology in patients <45 yo (pain with patellofemoral joint palpation and compression of patella against femur)

- XR imaging: if trauma <1w, XR indications per **Ottawa Knee Rule** - Sn 98%, Sp 49% (Annals 2004;140:121)
  - If eval of chronic OA: get weightbearing views of both knees; patellar view for patellar problems
- MRI: if suspecting fracture, infection, or internal derangement (e.g. ACL, meniscal tear in younger patients) *or* pain refractory to 4w conservative care. *Asymptomatic meniscal tears:* 13% <45 yo, 36% >45 yo (Clin Ortho Rel Res 1992;282:177)
- Rx: all benefit from rest, ice/heat, NSAIDs (topical/PO) ± APAP, compression, PT, wt loss. For mod-sev OA, young ACL tear, or any pain refractory to conservative tx, consider surgery. For bursitis, popliteal cyst, or IT band, consider steroid injection

SHOULDER PAIN (PCOI)

- General approach: r/o shoulder mimics, then rotator cuff pathology, then bursitis, impingement, OA or tendinopathy

Etiology	History Findings	Physical exam
Shoulder Mimics	Consider cervical/neck pain, biceps pathology, cardiac or GI radiation	
Rotator Cuff	- Acute = trauma - Chronic = age, acromial spurring, overuse - Tendinopathy, partial or full thickness tears - Pain & weakness, often with overhead arm use - Ortho referral often needed	- ↓ROM. Painful arc, impingement - **Internal lag test**: bring dorsum of patient's hand against lumbar region of back. Take forearm and hand away from the back (~20°). Ask pt to maintain position while supporting elbow. ⊕ if not maintained - **External lag test**: externally rotate shoulder 90°, flex elbow 90°. Ask pt to maintain position. ⊕ if not maintained - **Drop arm**: abduct arm to 90°. ⊕ if cannot smoothly adduct shoulder to waist-level - **Neer**: pronate forearm (thumbs point backwards), bring shoulder to full forward flexion. ⊕ if pain - **Hawkins**: flex shoulder to 90°, flex elbow to 90°, and internally rotate the shoulder. ⊕ if pain - **Ext rotation** (teres minor, infraspin): flex elbow 90°, externally rotate shoulder against resistance. ⊕ if pain - **Empty can** (supraspin): flex shoulder to 90°, internally rotate forearm. ⊕ if pain w/ resistance of downward push
Subacromial Bursitis	- Referred pain to deltoid - Overuse, heavy lifting	- Pain w/ arc 60°-120° abduction ± impingement - ⊕ Neer & Hawkins
Glenohumeral OA/ Adhesive Capsulitis	- OA: aching, stiff; age >60 - Capsulitis: ↑risk w/ DM, thyroid disease, immobilization; age 40-60	- OA: crepitus - Capsulitis: loss of active/passive ROM in all planes
AC Joint Pain	- Young: traumatic sprain, fall with separation - Older: AC evolves into OA & impingement	- Pain, tenderness, swelling over AC joint - ⊕ cross arm test

- Imaging: none for bursitis. **XR** if h/o trauma c/f fracture or dislocation, gross deformity, exam concerning for OA, RTC tear or joint involvement. Get true AP of glenohumeral joint, axillary lateral, & "Y view" of AC joint w/ stress views for trauma. **MRI w/o contrast** in pts w/ ⊕ internal/external lag tests, r/o full thickness RTC tear, previous abnl XR, persistent pain despite 2-3mo of conservative tx
- Rx: **conservative tx** w/ activity avoidance, NSAIDs (Topical/PO), PT/home exercises ± short-term steroid injections; **surgery** for refractory instability, labral/full RC tear, AC joint separation

LOW BACK PAIN (Acute LBP PCOI)

- Incidence/Prognosis: 84% lifetime acute back pain, 50% sciatica (Mayo Clin Proc 2015;90:1699); 75-90% improve over 4 weeks
- PE: palpation of midline & paraspinal muscles, ROM spine/hip, LE strength/reflexes (L4-5 = foot dorsiflex; L5-S1 = foot plantarflex, ankle reflex), rectal tone (if c/f cauda equina), SLR/crossed SLR (pain radiates below knee, often to heel, when straight leg raised while supine; crossed SLR is radicular pain in *opposite* leg, ↑Sp)

	Origin	Signs and Symptoms
Nonspecific MSK (85%)	Paraspinal muscles, ligaments, discs, facets	*Muscle spasm:* paraspinal muscle tenderness w/ acute onset, usually unilateral. *Disc*: young, ↑ w/ spine loading (i.e. sitting). *Facet*: >40 yo, ↑ w/ extension, ↓ w/ sitting
Radicular/ Spinal stenosis (7%)	Disc herniation w/ nerve compression (90% L4-S1), spinal stenosis	*Sciatica* 95% Sn, 88% Sp for herniation: leg > back pain w/ dermatomal distribution of lancinating/burning pain, SLR ⊕. *Spinal stenosis* causes neurogenic claudication: leg pain worse with walking (esp downhill) better with sitting/leaning forward
Specific spinal disorder (8%)	Vertebrae, discs, endplates, SI joints, facet joints	*Compression fx*: older, trauma, osteopenia, steroids. *SI pain*: MVA/falls, rheum. *Inflammatory*: AM stiffness, night pain. *Cancer*: PMH, weight loss, night pain. *Infection*: fever, night sweats, IVDU, immunosuppression

- Imaging: **early MRI** or XR if **RED FLAGS** – focal severe/progressive neuro deficits, cauda equina sx (b/l weakness, urinary retention/incontinence, saddle anesthesia); trauma; c/f fracture, osteopenia risk (age >50 or <20, PMH, steroids); c/f CA or infxn
  - Otherwise, **defer imaging until after initial 4-6w** tx (Annals 2007;147:478; Choosing Wisely) as herniation, disc bulging, DJD common findings (Am J Neuroradiol 2015;36:811). See STarT Back Screening tool for further guidance
- Possibly effective and lower-risk therapies:
  - **Avoid bed rest**. Explore social/psychological stressors, psych comorbidities, coping mechanisms
  - **Non-pharmacologic**: acute: heat/cold, massage, acupuncture; chronic: yoga, CBT, mindfulness, rehab (Annals 2017;166:514); **PT & exercise** (demonstrated benefit in sciatica (Annals 2021;174:8), though not other acute LBP)
  - **NSAIDs** (ibuprofen 400-800mg TID or naproxen 220-440mg BID) are first line for limited duration if no contraindication
  - *Muscle relaxants*: can add limited supply for acute pain if NSAIDs alone ineffective (JAMA 2015;314:1572)
  - *Duloxetine and TCAs* for **chronic** LBP; second line after NSAIDs (Annals 2017;166:480)
  - *Epidural steroids* (Pain Med/PM&R): for radicular pain refractory to 6w tx - limited evidence, benefits likely limited, short-term
- Therapies with questionable evidence and/or higher risk of harm:
  Acetaminophen: if NSAIDs contraindicated; but little e/o effectiveness (Lancet 2014;384:1586). *Oral prednisone taper* for acute sciatica: inconclusive evidence (Annals 2017;166:480). *Gabapentin, pregabalin*: option for sciatica though efficacy inconclusive (NEJM 2017;376:1111). *Opioids (see below):* limited evidence of effectiveness & ↑risk of harm (JAMA 2018;319:872). *Surgery:* short-term sx relief in disc herniation w/o clear long-term benefit, ↑side effects in spinal stenosis w/o e/o improved fxn

Foot and Ankle Pain (PCOI)

Etiology	History and Physical	Dx and Tx
Ankle sprain	- Trauma history - Pain/instability/swelling, bruising, focal tenderness over ligament (ATFL most common); squeeze test to r/o syndesmotic sprain	- Imaging: use **Ottawa Ankle Rule** (Sn 96%) - Ice, elevation, rest followed by exercise (consider PT) - Grade I (stretch, no tear): elastic wrap; grade II (partial tear, swelling, bruising): aircast or other splint; grade III (complete tear, unstable): casting, sports med/ortho c/s
Achilles tendinopathy	- Overuse or change in activity common - Pain & thickening at insertion or 2-6cm proximally; calf squeeze to r/o complete rupture	- MRI only if uncertain - Rest, ice, tendon support, PT - Surgical c/s for complete tear
Stress fracture	- Overuse; more common in ♀ esp if amenorrheic, underwt (rel caloric deficiency/overtraining syndrome) - Insidious onset of pain after exercising, ± focal tenderness on exam (tibia > tarsal > metatarsal)	- XR insensitive esp early in course; if ⊖ MRI may be req - Rest/non-wt-bearing 2-6w - Consider ortho c/s if high risk for nonunion (anterior tibia, navicular, talus, 1st or 5th metatarsal)
Plantar fasciitis	- Assoc w/ overuse, pes planus, overweight - Sharp anteromedial heel pain with activity after rest	- If uncertain, US may show thickening - Ice, stretching, NSAIDs, heel cups/OTC orthotics

Ddx: tarsal tunnel, **Charcot foot** (>40yo, obesity/neuropathy, swelling w/ minimal pain), hallux valgus ("bunion"), hallux rigidus (OA of 1st MTP), interdigital neuroma, non-Achilles tendinopathy, arthritis, gout/CPPD, derm (corns, calluses, warts, paronychia)

Long-Term Opioids for Musculoskeletal Pain

- **Before prescribing longer-term opioids**: (NB limited evidence; high risks of hyperalgesia, tolerance, dependence, addiction)
  - Exhaust non-opioid options. *Avoid BDZ, hypnotics*. Screen for OSA, SUD, mental health. Stress **complete pain relief is unlikely**. Set functional goals. Perform **risk assessment** (SOAPP-R). **Check PDMP**. Obtain prior records, speak to prior prescribers
  - **Pain agreement** (PCOI form) is **required**. MA law: *Must check PDMP and limit 7 days for initial opioid prescription.* Discuss **6-8w initial trial** & safe use, storage, & disposal of opioids. Educate that random UTox and pill counts are for pt safety. Agree that *single prescriber* will Rx. Rx on 28d cycle ending on weekday to facilitate refills. **Rx naloxone**
- **Follow-up for longer-term opioids**: See at least q1-3mo to review pain/function, side effects, adherence
  - **Discontinue opioids if no significant benefit at 6-8w**: significant side effects, risk > benefit, non-adherence
  - *Caution prescribing >50mg/d morphine equivalents (MME), avoid >90 MME (**c/s pain**)*
  - Early refill requests should trigger appointment to assess reason, obtain tox screen, discuss use

Primary Care — Immigrant & Refugee Health

MEDICAL EXAMINATION (CDC)

Interpreter Services: In person - x66966, p27403 (M-F 7a-8p; S/Su 8a-6:30p) or via phone service [617-643-3344 Pin #1050]. Speak in **short** sentences & make sure to address the patient (not interpreter) when speaking.

History: obtain prior medical records if possible

- SHx: country of origin, travel hx, transit countries, residence in refugee camps/detention centers, time living in US, family structure/hx of separation, food security, housing stability, home/neighborhood safety, education/**literacy**, occupational hx
- PMHx: chronic diseases (incl. pain), surgeries, cancer screens, ♀ OBGYN hx, sexual hx, meds (incl traditional/herbal remedies), smoke/toxin/lead exposures, tobacco/substance use (incl. those legal in country of origin; inform of legality differences in US)
- Mental health: screen for PTSD, anxiety, MDD (on 2nd visit to ↓re-traumatizing). RHS-15 is a consolidated screening tool.
- ROS: fever, wt loss, night sweats, respiratory concerns, diarrhea, abdominal discomfort, pruritis, skin rashes/lesions

Physical Exam: reassure patients this exam is for their health & not regulatory purposes

- Vision, dental, hearing, BMI, BP. Eval for murmurs, hepatosplenomegaly, LAD, skin lesions (rashes, trauma, nutrient deficiency)
- See PCOI for low-cost referral options for dental and eye care: → "Health Care Access"

Vaccinations: if no documentation (translation guide), assume not vaccinated (see *Health Screening & Maintenance*)

- Can check titers for MMR/VZV/HAV. Incomplete HBV vaccination may result in transiently elevated titers. Assess need for polio.

Screening and Labs:

- Gen: CBC/diff (eos, anemia), UA (hematuria), BMP (glucose, renal dz), ♀ hCG, lead screen if preg/lactating/taking medications, HepB/HepC screen; age-appropriate screens (lipids, HIV, etc.)
- STIs (see *STI*): syphilis, HIV, GC/CT if ♀≤24+sexually active or ♀>24+RF
- TB: ask yearly about sx, recent travel, sick contacts; retest PRN (see *Tuberculosis*)
- Malaria: Rx if from Sub-Saharan Africa w/o pre-departure Rx or from endemic country w/sx (Rx resistance info here). If preg/breastfeeding, Dx first (do not Rx empirically). Obtain thick/thin smears or PCR (↑Sn if no sx)
- Intestinal/tissue invasive parasites: varies by country & pre-departure tx. See CDC guideline. No empiric ivermectin if from *Loa loa*-endemic country
- Micronutrients (Fe, D, B12, etc): if malnutrition, anemia, h/o food insecurity
- Misc: Use CDC regional profiles or CareRef for recs for specific demographics

Infection*	Signs & Symptoms
Strongyloidiasis, filariasis, schistosomiasis	Peripheral eosinophilia
Schistosomiasis	Hematuria, ♀ infertility, chronic pelvic pain
Malaria, schistosomiasis	Splenomegaly
Mycetoma, onchocerciasis, other filarial diseases	Chronic rash or itching
Chagas disease	Esoph. dysmotility, HF, conduction dz
Neurocysticercosis	Seizures, CNS sx

LEGAL CONSIDERATIONS (Boston-area legal services, MGH Chelsea LINC referral if pt @ MGH Chelsea CHC)

- **Do NOT** document immigration status in EMR
- MassHealth eligibility is NOT contingent on immigration status. Refer all uninsured pts to PFS. Multilingual videos for pts on the ACA
- Know your Rights re: ICE: multilingual infographics from Immigrant Defense Project & Immigrant Legal Resource Center
- Asylum screening questions (yes/no answers sufficient; obtain only as much detail as necessary to refer for legal support; re-telling or re-living experiences can be re-traumatizing & asylum seekers will have to tell their whole story to lawyers/doctors in the future)
  - What led you to leave your home country?
  - Were you ever a victim of violence or (verbal, sexual, physical) abuse there?
  - If so, was it due to your religion, race, political beliefs, nationality, or particular social group (gender, sexual identity)?
  - If so, did you face violence from anyone working for the government, military, or police?
    - If yes → refer to legal organization above, PAIR, or the MGH asylum clinic
- Resources on conducting asylum evaluations and working with asylum seekers
- Resources within Boston area: Refugeography (Google map of various food pantries, job training, ESL, social support services, etc.)
- Additional tips: **Travel**: undocumented pts will now be able to apply for driver's license (DL) in MA (H4805), however, DL will likely not meet REAL ID requirements for air travel (to start: 5/7/25) – risk being detained by CBP agents stationed at any US international airport if trying to fly; **Legal**: can support pt's petition for legal status by providing documentation re: medical need for legal status (coordinate w/legal team if pt/team desires); **Advocacy**: consider joining Asylum clinic and/or IHC groups

Immigration Statuses	Details
Lawful Permanent Resident (LPR)	**Green card** recipient; pathway to citizenship. Family can get green card through "family based" immigration
U-Visa, T-Visa VAWA	Eligible if victim of human trafficking (T) or victim of certain types of crime (U). Violence Against Women Act: eligible if abused by spouse, child, or parent who is LPR/citizen
Temporary Protected Status (TPS)	Short list of countries where conditions preclude safe return. Cannot be deported while country of origin listed
Cancellation of Removal	Based on exceptional hardship anticipated to self or LPR/citizen, spouse, parent, child if deported; ineligible with certain criminal convictions
Asylum	Well-founded fear of persecution based on race, religion, nationality, membership in social group, or political opinion. Application due w/in 1y of date of entry. If granted, may apply to spouse/children if they are in US
Refugee	Same legal standard as asylum, based on persecution or well-founded fear, but granted prior to arrival in US. Maximum set annually by President (no limit to asylum)
Medical Deferred Action	Temporary reprieve from deportation for immigrants facing life-threatening medical conditions & other humanitarian circumstances
Withholding of Removal	Asylum/CAT/Withholding all part of same application. No 1y rule. Ineligible with certain criminal convictions. No path to citizenship
CAT	Convention Against Torture: similar to Withholding, but still eligible with criminal convictions
Undocumented	Patients should seek legal counsel to check for options to apply for alternative statuses

Alex Hoffner-Heinike & Esdras O. Rodriguez

Primary Care Climate Change & Health

Climate Change Drivers (NASA, CDC): **↑atmospheric CO_2 & other greenhouse gases 2/2 human activities**

↓

Principal Climate Effects (USGCRP CSSR 2017; IPCC AR6 2021):
↑temp, ↑sea level, precipitation pattern changes, ocean acidification, extreme weather

Mediators of Climate-Related Health Risks (NEJM 2019;380:263)

Access to quality healthcare	Baseline air & water quality	Geography	Poverty & housing
Age & sex	Baseline nutritional status	Occupation	Racism & discrimination
Agricultural practices	Ecosystem & land use change	Pre-existing health conditions	Warning systems

	Extreme heat	Poor air quality and increasing allergens	Climate-sensitive infectious disease	Extreme weather	Imbalanced water quality and quantity	Food insecurity
Health Effects	- Early death - CVD/resp dz exacerbations - Heat stress nephropathy - Fluid/ electrolyte disturbances - Suicide - Mental health - ↑risk congenital heart defects	*PM2.5* (particulates ≤2.5μm diameter): - Early death - CV disease (NEJM 2021;385:1881) - Worsened resp dz - Low birth wt *Ozone:* - Early death - ↑ED visits *Aeroallergens:* -↑asthma/allergy	- ↑habitability for Ixodes ticks → expanded Lyme distribution - ↑vectorial capacity for Aedes spp mosquitos → ↑dengue & malaria - ↑waterborne dz (Vibrio, Leptospira, Shigella, Campylobacter)	- Tropical storms: direct injury, trauma, flooding - Wildfire: burns & injury, inhalational injury, produces PM2.5 (see left) and other pollutants that can spread internationally	- Drought: resp effects of dust inhalation - Water insecurity → ↓nutrition, ↓sanitation, ↑susceptibility to violence - Flooding: ↑allergenic molds, diarrheal diseases, toxic algal blooms	- ↓nutritional content of staple crops - ↓productivity of fisheries - Undernutrition, underweight, & stunting - ↑susceptibility of food to spoilage & pests
Secondary Impacts	- Desertification - Missed work, 2˚ economic impact - Power outages	- Missed school, workdays -↑healthcare costs (Health Aff 2020;39:2113)	-↑strain on public health systems for dz control -↑abx resistance w/ ↑temp (Nat Clim Change 2018;8:510)	- ↑cost of disaster relief & recovery - Disrupted health care delivery	- ↓crop yields 2/2 precipitation Δ, salt water intrusion - Wildfire risk - Forced migration	- ↑frequency of conflict - ↑food prices, ↓purchasing power of vuln. populations

TREATMENT

Patient-Centered Actions	**Counsel Patients on Climate & Health Co-Benefits**
	• *Educate patients:* help patients understand links between climate and health (Ann Intern Med 2021;174(3):417), develop an extreme heat plan (CDC Guide, Boston Guide) & disaster-preparedness (PlanetReady, ClimateCrew) • *Co-Benefits*: actions that both improve health & mitigate emissions that drive climate change. Examples: o ↓Red meat consumption → improved CV/renal health, ↓emissions (in 2017, excess red meat consumption contributed to 990,000 deaths worldwide, & emissions from beef were >400kg CO2e/person) o Active transportation → improved CV health, ↓transport-related pollution & emissions (BMJ 2020; 368:l6758) o Inhaler Prescribing: MDIs use HFA propellant w/ potent global warming potential (GWP), MDIs have 10-37x GWP of matching DPIs. Prescribe DPIs when able, control asthma effectively to limit use of SABA, prescribe smaller canister SABAs (6.7g) to limit HFA release (BMJ 2019; 9(10):e028763)
Institutional Actions	**Improve Health Care Delivery in a Changing Climate**
	• Discuss the impacts of climate change w/ colleagues; Climate Resources for Health Education has slides/educational cases about the effects on most organ systems which are available for use in presentations • Improve resilience: U.S. Climate Resilience Toolkit: best practices for US health care facilities to withstand climate impact • Deliver climate-smart healthcare (NEJM 2021;385:2117): US healthcare-associated pollution comprised ~8.5% US GHG emissions & drove comparable disease as deaths from preventable medical errors (Health Aff 2020;39:2071). - Health Care Without Harm & Practice Greenhealth (free membership for MGH residents): resources to improve resource stewardship, decarbonize energy sources, & procure food & materials sustainably
Policy & Advocacy Actions	**Example Advocacy Topics in Climate and Health**
	• *Paris Agreement:* limits warming to 2˚C above pre-industrial levels, with further goal to limit to 1.5˚C in recognition that 2˚C would be catastrophic for certain populations (IPCC SR1.5 2019). Warming is on track to exceed 2.7˚C by 2100 (UNEP EGR 2021). Current policies and mitigation efforts continue to fall short with global emissions reaching a record high (once again) in 2022 (Lancet 2023; 402:2347) • *Equity is critical:* people least responsible stand to suffer most (Health Aff 2020;39:2056). Locally, Black and Latinx Americans inhale disproportionately more PM2.5 than is caused by their consumption (PNAS 2019;116:6001) due to intentionally racist practices such as redlining (EST 2022;9,4,345–350) • Massachusetts Climate Action Network is supporting multiple bills currently in MA state legislature

Read NEJM 2019;380:209 & ACP Toolkit for further resources for physicians, patients, and policymakers; PCOI page for tips in primary care and handouts for discussion with patients

Shraddha R. Damaraju

Social Determinates of Health (AAFP EveryONE Project)

Accounts for 30-55% of health outcomes with up to 20-year gap in life expectancy between counties with lowest and highest life expectancy in the US. SDH primarily influence health outcomes through limiting opportunities to live a healthy lifestyle or chronic stress (JAMA 2017; 117:1003). Structural racism limits opportunities through discriminatory practices in labor, housing and educational systems with racism and stress being shown to affect both mental and physical health outcomes (Lancet 2017; 389:1453).

Economic	Environmental	Education	Food	Community	Health Systems
Employment Income Expenses Debt Medical bills	Housing Transportation Safety Parks Playgrounds	Literacy Language Early ed. Higher ed. Vocational	Hunger Food deserts Availability of healthy options	Social integration Support Discrimination Racism Stress	Insurance coverage Provider availability Linguistic/cultural competency Quality of care

↓

Health Outcomes
mortality, morbidity, life expectancy, health expenditures, functional limitations, health status

Strategies to Addressing Health Inequity

1) Understand patient's community (County Health Rankings and Roadmaps); screen for SDOH (useful dot phrase: .SDOHSCREEN, if positive refer to MGH SDoH Services aka "Ambulatory Referral to MGH SDH")
2) Consciously address implicit bias (Harvard Project Implicit); reflect on gut reactions, ask if they are rooted in implicit bias
3) Address patient health literacy; utilize in-person interpreter services when available, schedule longer visits, employ teach back method, utilize dot phrase .MEDSS for a framework to optimize medication adherence.
4) Identify and utilize resources within your clinics to address SDOH; AAFP Neighborhood Navigator, 211, and FindHelp can help identify local resources

Insurance Coverage

- Open enrollment: limited time when one can buy a new insurance plan, varies by employer and insurance system; MassHealth ~Nov-Jan.
- Patient Financial Services can assist patients, both inpatient and outpatient, with applying for state-funded programs such as MassHealth and Health Safety Net: 617-726-2191.
- MassHealth: federal and state funded healthcare coverage, MA's interpretation of Medicaid and CHIP; can apply online (if age <65), by mail or fax, will take 45-90d for approval; must renew households annually
  - Basic eligibility requirements: MA resident, eligible citizenship/immigration status, valid SSN
    - Can apply for MassHealth Limited for patients who have an immigration status that keeps them from getting more services.
  - Several coverage options available with eligibility for age <65y determined by comorbidities and income, ranging from ≤133-300% federal poverty limit (FPL); age ≥65y eligible if income ≤100% FPL, more lenient for disabled seniors

Primary Care Disability Competent Care

Authors Comments: Please note that this is an incredibly important and evolving field, which lacks substantial data, publications, and amplification of voices of individuals with disabilities. We write this page with humility and awareness that we are constantly learning how best to support and care for our patients with disabilities. We would welcome any feedback. This White Book page is largely adapted from: Kripke C. Adults with Developmental Disabilities: A Comprehensive Approach to Medical Care. Am Fam Physician. 2018;97(10):649-656.

DEFINITIONS, MODELS, LANGUAGE

- Disability: Differences in cognitive and/or physical function in which individuals benefit from support in areas of major life activity; ie self-care, language, mobility, self-direction, ability to live independently and economic self-sufficiency. Am Fam Physician. 2018;97(10):649-656
    - Disabilities are diverse. They can be related to, but not limited to: developmental conditions, genetic conditions, injuries, strokes, chronic diseases (eg diabetes), physical and neurologic disorders and psychiatric disorders .Blind/deaf Ablism
- There are many models of care for individuals with disability (i.e medical, social, bio-psychosocial) Current medical practice is moving towards centering the Neurodiversity & Social Model of care. Am Fam Physician. 2018;97(10):649-656
    - **Medical model**: Disability is a problem of the person, directly caused by disease, trauma or other health condition, which requires medical care. Management of disability aims at cure or the individual's adjustment and behavior change.
    - **Neurodiversity Model**: Neurocognitive differences are valued components of human neurologic diversity.
    - **Social Model**: Emphasizes that disability is a socially created problem, not an attribute of an individual. Focuses on improving positive experience in society, emphasizes inclusion and accommodation in physical & social environments
- Individuals with disabilities face tremendous amount of discrimination in society, including the healthcare system.
    - Rejection of medical model of disability, which treats disability as an illness that needs to be fixed or overcome.
- Disability Competent Care: A model that focuses on caring for the individual beyond the disability, rooted in 3 core values: "1) the individual needs of the participant, 2) respect for the participant's choices, and 3) the elimination of medical and institutional bias." (RIC DCC Model)

APPROACH TO HEALTHCARE MAINTENANCE, SEXUAL AND MENTAL HEALTH

- **Healthcare Maintenance**: See section on **Age Appropriate Screenings**.
- Adults with disabilities face profound healthcare inequities. They are at higher risk for heart disease, diabetes, obesity & smoking compared to adults without disabilities (CDC Disability & Health in MA 2023)
- Clinicians have conscious/unconscious biases and make assumptions about adults with disabilities' GOC and QoL that contribute to disparities in health outcomes. (Health Aff (Millwood). 2021;40(2):297-306)
- Conduct annual physicals, as medical conditions tend to be underrecognized and undertreated, particularly among nonverbal patients. (see Table from Am Fam Physician. 2018;97(10):649-656)
- At **initial encounter**, conduct baseline assessment of function, with a focus on: a) cognition b) communication c) sensory function (eg vision, hearing) d) neuromuscular function e) seizure threshold (if applicable) f) mental health. Acute illness among individuals with disabilities often presents as a change from baseline function. (Am Fam Physician. 2018;97(10):649-656)
- **Sexual Health**: Offer comprehensive sexual and reproductive health services. Do not assume that adults with disabilities are not sexually active, do not wish to become pregnant or are not at risk for STIs.
- **Mental Health**: Adults with disabilities report mental health distress 4.6x more frequently than adults without disabilities. Prioritize mental health screenings, treatment, and lifestyle modifications to promote wellness (eg sleep, healthy weight, physical activity as able) (MMWR 2020:69(36))

Common Unrecognized or Undertreated Medical Problems in Persons with Developmental Disabilities

Medical problem	Possible presentations in nonverbal patients
Abuse or neglect	Aggression, defiance, withdrawal, meltdowns
Constipation	Small stools, liquid stools, soiling, rectal digging, urinary retention
Deconditioning	Worsening contractures, constipation, decreased mobility
Dental caries or periodontal disease	Feeding problems, head banging, agitation
Drug or alcohol use	Memory loss, confabulation, unsteady gait
Dysphagia/microaspiration	Shortness of breath or cough with or after meals, slight elevation of body temperature, tachycardia
Endocrine or metabolic disorders (especially hypothyroidism and syndrome of inappropriate antidiuretic hormone)	Sedation, changes in drug metabolism
Kidney or gallstones	Urinary retention, irritability
Medication adverse effects/polypharmacy	Behavior problems, sedation, paradoxical reactions, atypical drug metabolism
Nutritional deficiency	Amenorrhea, spontaneous fractures, constipation, pressure sores
Occult fractures or injuries, arthritis, nerve compression, osteoporosis	Changes in mobility, sedation
Pain syndromes	Irritability; insomnia; decreased participation; change in function; aggression; scratching, banging, or touching the body part that hurts
Rashes	Irritability
Seizures, including less common seizure types	Emotional lability, unresponsiveness, fatigue, automatisms
Sleep apnea	Elevated hematocrit, sedation
Urinary retention	Grabbing genitals, abdominal distention, urinary tract infections
Urinary tract infections	Irritability, aggression, sedation
Vision and hearing deficits	Decreased participation or mobility; easily startled; aggression

LANGUAGE AND COMMUNICATION

- Commitment to person-centered communication and patient autonomy, communicating and acting with humility towards patients and their families.
- Speak directly to pt regardless of ability to respond. Use of aides to enhance communication: pictural language, voice amplifiers, demonstrations, alternative formats (large print, braille). View UCSF Communication Toolkit for more resources.
- **Language matters**: Avoid terminology such as "handicap," "mental retardation," and "wheelchair bound" or "confined to a wheelchair." Preferred terms are "disabled," "intellectual disability," and "wheelchair user"

Examples of patient and family centered language (adapted from: *Am Fam Physician.* 2018;97(10):649-656, please view for more examples)

Common Pitfall	Respectful Alternative
Speaking to supporter: Since she is non-verbal, can you share what brings her in today?	Speaking to patient: Can you show me how you say yes and no? Are you in pain? Thank you for sharing. I would like to gather some more information. Is it ok if I ask your __ (supporter)?
To supporter: Your son is so lucky to have you—you are a super dad!	Patients and their families both deserve support. What types of support do you (supporter) need?

ACCOMMODATIONS AND SERVICES

- FMLA: Family and Medical Leave Act provides 12 weeks of unpaid leave per year. Can be used for personal illness, carrying for a family member an illness, parental leave after birth/foster/adoption.
- Short-Term Disability: Replaces a portion of income for 3-6months for patients who develop illnesses, disabilities, or injuries not related to jobs
- Long-Term Disability: Replaces a portion of income if patient cannot work for >90 days
- Social Security Disability Insurance: provides monthly payments to individuals who cannot work due to their disability

Amanda Jowell & Lisa Lezzoni

Consultants Calling Consults

TIPS FOR CALLING CONSULTS

- **To do BEFORE you call**:
  - Place **order** in Epic for consult
  - **Know your patient**: review the H&P/chart and *see/examine the patient*; recommend reviewing last clinic & operative notes if applicable (Notes → Filters → Specialty); for all below, mention any outpatient providers
    - **GI**: melena/hematochezia, current/prior H/H, plts, coags, transfusions, past EGD/colo, vitals, IV access, NSAID/ASA use, rectal exam findings; for cirrhosis: any prior work-up, social history, complications, decompensation
    - **Cards**: recent and old ECG, telemetry, prior stress/echo/cath (know anatomy), dry weight, biomarkers, current cardiac meds
    - **Renal**: baseline Cr, CKD stage, on/off HD, dialysis access, electrolyte mgmt, current UOP, nephrotoxins
    - **Onc**: known cancers w/ stage/tx history, clinical trial history, biopsy results (for new dx), current anticoagulants, special slide; if on immunotherapy, usually on SIC (Severe Immunotherapy Complications) service list at MGH
    - **ID**: current/past micro data, possible sources, current/prior abx (incl # of days), fever curve, hardware, travel, exposures
    - **Pulm:** imaging results, social hx, prior work-up (e.g., autoimmune), prior/current O2 requirements, PFTs
  - **Know your question** – Bigelow JAR should specify consult question in task list. *If not there, ASK. It is always OK to clarify*
- **To do DURING the page/call**:
  - Call as early in the day as possible (ideally before noon), find out how to page using the paging directory
    - At MGH: paging directory → find "On Call Directory"
  - In your **page** to consulting team, include: **pt name, MRN, location, call back #, brief consult question +/- level of urgency**
  - Avoid "curbside" questions unless official curbside consult service. If specific question about management, call a formal consult.
  - Tell the consultant the **One-Word reason for your call** (i.e. hematochezia, hemoptysis, hyponatremia etc.) followed by a **brief HPI,** a clear **explanation of the team's thinking,** and a **clear and specific question**
- **To do AFTER the call**:
  - Invite the consultant to find you to relay their recommendations or tell them who will be covering for you
  - Consultant will often provide prelim recommendations on phone, follow-up recommendations in documentation/note later

CALLING EMERGENT CONSULTS

- **Surgery**: STAT = imminently life-threatening emergency (e.g. lost airway, hypotensive from hemorrhage); URGENT = high concern for urgent surgical question (e.g. acute abdomen, perforated bowel, etc.)
  - Page *"Churchill Senior on call"* under **Emergency General Surgery(Churchill)**
- **Psychiatry** (e.g. pt actively trying to leave AMA w/ unclear capacity; security concerns, major behavioral issues)
  - 8am-6pm: p33061 (Emergency Consult Resident). If weekend/Holiday: p17911 (weekend rounding psychiatrist)
  - 6pm-8am: Call APS (4-7688) or page APS resident at 27792
- **Toxicology (ingestions/overdoses/exposures/interactions)**: call Poison Control Massachusetts (617-355-6607 or 800-222-1222).
- **Cardiac Surgery**: page the Attending On Call. **Thoracic Surgery**: page the Fellow on Call. **Vascular Surgery:** pg 21469.

CALLING SURGICAL CONSULTS AT MGH

- **The patient must be seen when a consult is called. Please try to call early or, if nonurgent, wait until the next day if late.**
- **In the ED**: ED surgery "pit team." They typically sit in Acute bay across from room #5 & are listed in Amion as ED Surgery Team
  - For patients in the Acute bay: pit senior (x44169; p13115). For patients anywhere else in the ED: pit junior (x44187; p20491)
  - Once the patient is on the floor, page PGY1 on the consulting team (identified in the consult note)
- **New surgery consult (floor or ICU):** page the senior resident of the appropriate surgical service
  - If patient known to an MGH surgeon, consult senior resident on that team to discuss
  - If patient not known to a surgeon, do your best to elucidate the appropriate team based on disease state (Baker surgery teams). When in doubt, contact the senior resident of the most appropriate team to further triage.
- **Follow up on GENERAL surgery consults:** page the PGY1 covering the consulted service
- **Cardiac Surgery consult** → if non-emergent (8:30am-5pm) place order. Also page NP at 30010 from 5pm-8:30am, weekends, and holidays.
- **Ortho consult** → page *"Floor resident"* at 20296 under "Orthopedics" or if ED consult, page 22566
- **Transplant Surgery consult** → page *"Resident"* under "Transplant Surgery"

CALLING OTHER SUBSPECIALTY CONSULTS

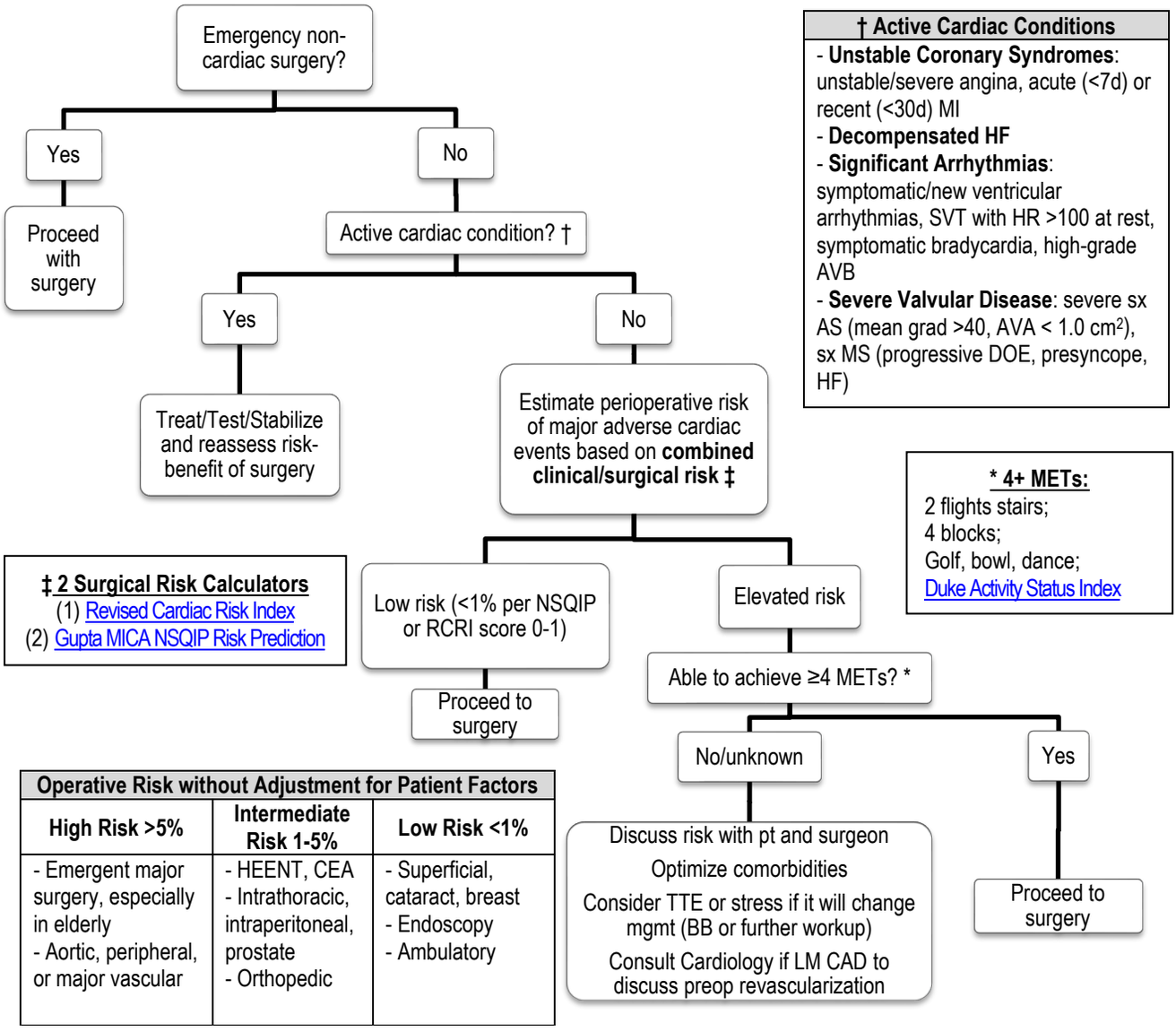
- **ACT (Addiction Consult Team)**: place consult in Epic (no need to call), page 29967 if need help overnight.
- **AMS (Anticoagulation Management Service)**: for established pts: p30104, or click AMS icon in Epic to determine existing AMS RN. For discharge – place Epic consult; if urgent or questions, page Discharge Pathway Service: p30104
- **Cardiology**: login to Amion under "mghcardiology" to identify appropriate fellow (link also in paging directory)
- **Chronic pain service** for refractory or cancer pain; for interventions (e.g., injections/ketamine/high dose PCA)
- **Acute pain service** for epidurals, periop pain.
- **Diabetes nurse educator**: service NP p20737; MD p14364
- **ENT**: page 22220. Backup/emergency number is 617-523-7900 (MEEI operator) and ask them to page ENT resident on call
- **Optimum Care Committee ("OCC," Ethics)**: page ethics support pager: p32097 (Mon-Fri, 8am-4pm, except holidays)
- **Ophtho**: p21004. Backup # 617-573-4063 (MEEI ED). Before calling *know if OK to* ***travel to MEEI*** *for exam & if* ***ok to dilate****.*
- **Psychiatry**: for non-emergent floor consult: order psych consult in Epic
  - *Weekday, Weekend Night, Holiday Night:* call CL coordinators (6-2984). These consults will be seen within 24 hours.
  - *Weekend or Holiday 8am-5pm***:** p17911 (weekend rounding psychiatrist)
- **Transfusion reactions**: page blood bank resident at 21829

PERI-OPERATIVE CARDIAC RISK STRATIFICATION AND RISK REDUCTION

GOAL: to **estimate risk, optimize**, and pause for cardiac testing regarding peri-operative cardiac events, ***NOT to "clear for surgery"***

- Peri-op cardiac events: **MI** (usually clinically silent, NSTEMI>STEMI, POD#0-3, not intraop), **CHF**, **VT/VF**, **cardiac arrest, death**
  - Major determinants include: (1) preceding condition of patient (2) risk of procedure (3) functional capacity
- Emphasis on risk stratification. **Very few patients need non-invasive/invasive testing,** only if testing would change cardiac optimization management (initiating medical management, PCI, Cardiac Surgery) even *in the absence of surgery*

PERI-OPERATIVE CARDIOVASCULAR EVALUATION FOR NON-CARDIAC SURGERY (adapted JACC 2014;64:e77)



Operative Risk without Adjustment for Patient Factors		
High Risk >5%	**Intermediate Risk 1-5%**	**Low Risk <1%**
- Emergent major surgery, especially in elderly - Aortic, peripheral, or major vascular	- HEENT, CEA - Intrathoracic, intraperitoneal, prostate - Orthopedic	- Superficial, cataract, breast - Endoscopy - Ambulatory

REVISED CARDIAC RISK INDEX (RCRI, GOLDMAN) (Circ 1999;100:1043; Can J Cardiol 2017;33:17)

- **Six independent predictors (risk factors) of major cardiac complications**
  1. High-risk noncardiac surgery (not a clinical RF but incorporated elsewhere in algorithm): OR 2.6
  2. CAD (MI, PCI, CABG, angina, nitrate use, ECG with pathologic Q waves, or ⊕ exercise stress test): OR 3.8
  3. HF (CHF, pulm edema, bilateral rales, or S3): OR 4.3
  4. Cerebrovascular disease (stroke or TIA): OR 3.0
  5. Diabetes mellitus with preop insulin therapy: OR 1.0
  6. Renal insufficiency with preop Cr >2.0 mg/dL: OR 0.9
- RCRI event rates were re-calculated (and partially validated) in 2017 after multiple trials included troponins ± emergent surgeries

Rate of cardiac death, MI, pulm edema, CHB, cardiac arrest/VF		
RCRI	1999 Event Rates (95% CI)	2017 Event Rates (95% CI)
0	0.4-0.5% (0.05-1.5) → ~0.5%	3.9% (2.8-5.4) → ~4%
1	0.9-1.3% (0.3-2.1) → ~1%	6.0% (4.9-7.4) → ~6%
2	3.6-6.6% (2.1-10.3) → ~5%	10.1% (8.1-12.6) → ~10%
≥3	9.1-11.0% (5.5-18.4) → ~10%	15.0% (11.1-20.0) → ~15%

Alternative Cardiac Risk Assessment (MICA, Gupta) (Circ 2011;124:381)

- Identified 5 risk factors predictive of *risk of STEMI or cardiac arrest* w/in 30 days of surgery:
  1) Type of surgery/procedure, 2) preoperative functional status, 3) serum Cr >1.5, 4) ASA class, 5) increasing age
- Compared to RCRI, **better** discriminative predictive value
- **Limitations**: likely underestimates actual risk because MI was defined in the study based on only ECG changes: STEMI or new LBBB; biomarkers were NOT monitored post-op, which is necessary to detect more than 50% of perioperative MIs

Preoperative Coronary Revascularization (NEJM 2004;351:2795)

- **CARP**: multicenter RCT of 510 high-risk vascular surgery patients, showed prophylactic revascularization w/ BMS/CABG conferred no survival benefit; data extrapolated to lower risk non-vascular/non-cardiac surgeries
  - Exclusion criteria: EF < 20%, unstable angina, LMCA disease > 50%, severe AS

Peri-operative β-Blockade and Other Cardiac Drugs

- **Evaluate for peri-operative β-blockade** (Circ 2014;130:278)
  - **Continue β-blocker**: if already taking for other indication (e.g. CAD, arrhythmia, HTN) for goal HR 55-65 (Class I, LOE C)
  - **Consider initiating β-blocker**: ≥3 RCRI RFs or intermediate/high risk preop test (Class IIb, LOE B)
    - ***Do not start a β-blocker within 24 hours of surgery!*** (Lancet 2008;371:1839; JACC 2014;64:2406)
  - **Uncertain role of β-blocker**: if ⊕ stress test or long-term indication without other RCRI risk factors
- **Anti-platelet**: (NEJM 2014;370:1494; Anesth Analg 2015;120:570)
  - 1° prevention: can generally be held prior to surgery
  - 2° prevention: continue ASA 81mg unless high risk of bleeding (intramedullary spine, intracranial, hip, knee, possibly prostate)
  - DAPT post-PCI: POBA <14d, BMS <30d, DES <6-12mo → discuss with Cardiology
- **ACEi/ARB**: pts have more transient peri- and post-op episodes of HoTN; **no diff** in death, post-op MI, stroke; ↑ or ↓ AKI unclear
  - Discontinue ACEi/ARB night before surgery (unless used for HF and BP ok). At MGH hold prior to cardiac surgery
  - Failure to restart ARB within 48h ↑30d mortality (Anesthes 2015;123:288)
- **Other**: consider holding diuretics, other anti-hypertensives should be continued perioperatively to goal BP <180/100 to avoid bleeding
- **Anticoagulation and bridging**: see *Anticoagulation Management*

VTE Prophylaxis (Mayo Clin Proc 2014;89:394)

- Postop VTE risk assessment: Caparini Score
- Non-orthopedic surgeries: those undergoing **general** or **abdominal/pelvic surgery** are at highest risk
- Orthopedic surgeries: **all pts at high VTE risk** 2/2 tourniquet time + immobilization; minimum duration 10-14d (35d if higher risk)

Peri-operative Monitoring and Considerations (NEJM 2015;373:2258)

- **ACS NSQIP Surgical Risk Calculator** can help estimate other post-operative complications including LOS, need for rehab, risk of non-cardiac post-operative complications (Am J Cardiol. 2018; 121:125)
- **ACS**: most MIs occur w/in 48h while patients are on analgesics that mask pain → some data show benefit of troponin monitoring (JAMA 2012;307:2295). Elevated post-op NT-proBNP can be used as a predictor of post-op MI and death (JACC 2014;63:170)
  - Myocardial injury after noncardiac surgery (MINS) commonly asymptomatic; variable recommendations for screening with ongoing studies → MINS is an independent predictor of 30-day mortality (Anesthesiology 2014;120:564)
- **AF**: may be a more important risk factor than CAD for 30d post-op mortality (Circ 2011;124:289). Associated with higher preop # of preexisting comorbidities and increased postop LOS, cost, and mortality (Am Heart J 2012;164:918), as well as similar thromboembolism and death risk to pre-existing NVAF (JACC 2018;72:2027)
  - If multiple episodes or lasts > 48h, recommend OAC and close follow up for further decision-making
- **Pulmonary Disease**: numerous risk factors for postoperative pulmonary complications, including COPD, OSA, pHTN, low albumin. Multiple risk calculators for different outcomes, including ARISCAT (Anesthes 2010;113:1338), Gupta (for resp failure), and Gupta (for PNA). Mitigation of risk usually supportive, including incentive spirometry and smoking cessation. Consider Pulmonology consult
- **Post-operative PNA**: ~20% mortality; pre-op CXR or PFTs not recommended because rarely change management
  - Risk factors: COPD, age >60, ASA class ≥II, albumin <3.5, poor functional dependence, weight loss >10% over previous 6 months (Annals 2006;144:575)
- **Renal dysfunction**: increased risk of complications in ESRD; AKI also a/w high morbidity and mortality (Ann Surg 2009;249:851)
- **ESLD**: increasing risk of perioperative mortality with increasing MELD & Child-Pugh scores. If Child-Pugh B, optimize VIBES & consider TIPS for refractory ascites. If Child-Pugh C, optimize, consider transplant, & discuss risk/benefit nonsurgical options (J Gastroenterol Hepatol 2012;27:1569; Clin Gastroenterol Hepatol 2020;18:2398)
- **Low albumin**: independent predictor of 30d post-op morbidity and mortality (Arch Surg 1999;134:36)

Consultants Dermatology

Before Consulting Dermatology: *upload photos of rash* *(ideally pre-treatment) to media tab of EPIC using Haiku*

- If consulting for drug rash, note exact timing of rash development and administration of suspect medications
- Note: Erythema in patients with darker skin types can present with a more violaceous or dark brown hue; textural changes are important to note. Applying gentle pressure to blanch involved skin or use of a bright light may accentuate subtle erythema.

Quick Steroid Guide
• Face/intertriginous areas: hydrocort. 2.5% cream, hydrocort. valerate 0.2% cream • Body: fluocinolone 0.025% cream if mild, clobetasol 0.05% ointment if severe → mid strength to super potent depending on severity • Scalp: 0.01% fluocinolone scalp solution or oil (dermasmoothe); oil better for dry scalp ***Counsel patients:*** Use BID x2 wks then 1 wk "off", avoid face (risk = skin thinning)

MGH topical steroid formulary by level of potency	
Super-potent	clobetasol 0.05%, betamethasone dipropionate 0.05%
Potent	fluocinonide-emollient 0.05%
Upper-mid strength	betamethasone valerate ointment 0.1%
Mid-strength	fluocinolone ointment 0.025%
Lower mid-strength	fluocinolone cream 0.025%, betamethasone valerate cream 0.1%
Mild	hydrocortisone valerate 0.2%, fluocinolone oil 0.01%
Least potent	hydrocortisone 2.5%, hydrocortisone ointment 1.0%
Over the counter	hydrocortisone cream 0.5%, 1.0%

Choice of vehicle: ointments ↑ potent, ↑ stickiness, ↓ irritation

Common Dermatologic Conditions

- **Allergic contact dermatitis**: appears as a geometric shape with well-demarcated borders (i.e. square tape). Usually localized but may generalize 2/2 autoeczematization (a.k.a. "id reaction", may also occur 2/2 tinea anywhere on the body). Identify and remove suspected trigger. Tx w/ high potency topical steroid for limited BSA (low to mid potency for face). Pred taper (>1wk) for more extensive BSA involvement.
- **Eczema/atopic dermatitis**: tx depends on severity. Intense BID/TID moisturization (plain hydrated petrolatum, Cetaphil®, CeraVe®). For affected areas, use mid-strength to super-potent topical steroids BID x 2wks. For face, use least potent to lower mid-strength steroids BID x 1-2wks. Scalp: mid- to high-potency steroid in solution, foam, or oil vehicles. Erosions/fissures: petrolatum or mupirocin ointment BID x 1-2wks if concerned for superinfection and/or MRSA positive.
- **Cellulitis**: consider **derm consult if not improved in 48h** to distinguish cellulitis mimickers (30% of cases)
  - Calculate ALT-70: 5-7 = 82.2% likely cellulitis; 3-4 = consider derm c/s if no improvement by 48h with abx. Consult reduces abx use + duration (JAAD 2017;76:618; JAMA Derm 2018;154:529). **Bilateral LE cellulitis is rare.**
- **Pressure injury/ulcers**: document in H&P with Haiku pics.
  - NPUAP Staging: 1) non blanchable erythema of intact skin, 2) partial thickness skin loss with exposed dermis, 3) full thickness skin loss, 4) full thickness skin and tissue loss. Can be unstageable due to eschar/necrosis
  - **Wound Nurse consult** for: stage 3-4 pressure injury, device related injuries, moisture associated skin damage, edema drainage management, special bed surfaces (i.e. clinitron, bariatric). **Wound Service consult** (Plastics/Vascular) for: acute wound issues such as limb ischemia, wet gangrene, any wound requiring OR debridement. Consider derm c/s to confirm etiology.
- **Intertrigo:** chronic inflammation in skin folds usually superinfected with yeast or bacteria. Candidal intertrigo →outlying papules or pustules. Eliminate friction, moisture, heat with wicking fabric (Interdry), barrier cream (zinc oxide paste), avoid powders when active. Topical azole antifungal BID to reduce yeast burden, caution with topical steroids in thin/occluded areas. Immunocompromised patients with intertriginous lesions should prompt concern for deep fungal infections JAAD 2021;17:92.

Other Dermatologic Conditions

- **Calciphylaxis**: extreme pain (may precede lesion), violaceous retiform patch/plaque +/- "woody" induration → necrosis, ulcer, eschar. Can appear at sites of trauma (injection sites, surgical debridement) JAAD;13:57.
  - Risk Factors: ESRD on dialysis (most common), warfarin, 1° hyperPTH, malignancy, prior bariatric surgery
  - Dx: skin biopsy (gold standard, not sensitive); Ca^{2+} x phos product, PTH; bone scan w/ increased uptake
  - Tx: normalize serum Ca^{2+}/phos/PTH via non-Ca based phos binders (i.e. sevelamer) and cinacalcet; Intralesional or IV sodium thiosulfate; treat 2° infections (death from sepsis), consider hyperbaric O_2 (consult MEEI Hyperbaric Medicine), pain ctrl, wound care (Medihoney), nutrition consult. D/c warfarin if possible; consider AC if appropriate. Calciphylaxis = indication for HD in CKD
- **Cutaneous GVHD**: skin pain/pruritus can precede eruption, acral → central; acute vs. chronic based on morphology, *not* time course
  - Acute: follicular erythematous papules. Chronic: morphology varies, can be dry and scaly (asteatotic), pruritic and erythematous (eczematous), thickened and raised (lichenoid), tight and thick (sclerodermoid), pigment changes and atrophy (poikilodermatous)
  - Stage 1: <25% BSA, stage 2: 25-50% BSA, stage 3: >50% BSA, stage 4: erythroderma w/ bullae (TEN-like).
  - Tx: immunosuppression with corticosteroids +/- cyclosporine or tacrolimus, supportive care
- **Immunotherapy toxicity:** result of t-cell activation; most common on PDL-1 inhibitors, highest incidence of adverse immune related effects are mucocutaneous (~50% of immunotherapy patients, ~2% severe (>grade 2)); usually managed outpatient; variable timeline
  - Wide range of severity (grade 0->3)/presentations: maculopapular/lichenoid → pruritis → psoriasiform → bullous, SJS/TEN
  - Derm and/or SIC consult warranted if not controlled w/ topical high potency steroids inpatient +/- oral pred 0.5-1mg/kg
  - Grade ≥ 2 = hold ICI + monitor, Grade >3 = hold ICI + dose reduction likely req. (SITC Guideline 2021).
- **Herpes simplex virus 1/2**: always confirm w/ DFA or PCR from vesicle base; cx possible but takes long to result

Nnenna Ezeh, Rebecca Gaffney, & Olivia Cohen

  - Uncomplicated orolabial: usually gingivostomatitis → acyclovir 400mg TID x7-10d; if recurrent → valacyclovir 2000 mg PO q12h x 1d or famiciclovir 1500mg PO x1 at sx onset; periocular skin involvement warrants ophtho c/s to r/o herpetic keratitis
  - Uncomplicated genital (immunocompetent): 1º ep (<72hr onset)→valacyclovir 1000mg PO BID x10d, acyclovir 400mg PO TID x10d, or famciclovir 250mg TID; recurrent eps (<24hr onset)→valacyclovir 500mg PO BID x3-5d or acyclovir 400mg PO TID x5d.
  - Complications: sacral radiculitis (acute urinary retention), proctitis (MSM).
  - Ppx for immunosuppressed patients: acutely immunosuppressed, e.g. transplant patients or patients with hematologic malignancies undergoing induction chemotherapy, HSV seropositive: acyclovir 5 mg/kg IV q8h X 7d → acyclovir 200-400 mg PO 3-5x daily x 1-3 mos; for prevention of recurrence in people living with HIV (NOT primary prevention): acyclovir 400-800 mg PO BID/TID or valacyclovir 500 mg daily or famciclovir 500 mg BID. Consider high lysine/low arginine diet to prevent HSV recurrence
- **Herpes zoster (shingles)**
  - Uncomplicated, <72 hr (immunocompetent): valacyclovir 1000mg PO Q8H x7d or acyclovir 800 mg PO 5x/d x7-10d
  - Disseminated: >20 vesicles and two 1º (non-adjacent) dermatomes; acyclovir 10mg/kg IV q8h; consider immunodeficiency w/u; droplet precautions
  - Immunosuppressed: acyclovir 10 mg/kg IV q8h; IVFs if hypovolemic/CKD to decrease risk of crystalline nephropathy; obtain DFA/viral culture; monitor for complications (PNA, encephalitis, aseptic meningitis, hepatitis)
  - Zoster ophthalmicus: urgent ophtho consult if c/f ocular involvement ("Hutchinson sign" = vesicle on nasal tip)
  - Post-herpetic neuralgia: risk ↓ w/ early antiviral treatment (<72 hr); if higher risk (≥50yo w/ mod-to-severe acute pain) consider preventive tx w/ gabapentin 300mg PO QD, titrate up to 3600mg QD, divided TID as tolerated
  - Consider post-episode vaccination
- **Erythema multiforme**: target lesions (well-defined, circular erythematous macules/papules w/ 3 distinct color zones + central bulla or crust) on palms/soles +/- mucosal involvement occurs within 24-72 hours; persist for 2wks
  - 90% triggered by infection (HSV, mycoplasma, GAS, EBV); less commonly drug rxn
  - Tx: treat underlying infxn, NSAIDs, cool compresses, topical steroids, antihistamines; systemic steroids only if severe
- **Erythroderma**: diffuse redness >90% BSA; caution: can progress to bullous/skin sloughing
  - Causes: psoriasis, atopic derm, cutaneous T-cell lymphoma (incl. Sezary), pityriasis rubra pilaris (islands of sparing), drugs
  - Work-up: detailed med rec, +/- HIV. Tx: derm c/s; liberal emollients, mid-potency topical steroids, antihistamines; fluids/lytes; monitor for 2º infections; d/c offending meds.
- **Purpura fulminans**: **"DIC in skin" = true emergency**; consult Hematology for possible factor replacement
  - Microvascular skin occlusion w/ platelet-fibrin thrombi → retiform purpura
  - Causes: infection (Strep, Staph, H. flu, N. meningitidis, Capnocytophaga, VZV, CMV, Babesia); catastrophic APLAS, CTD, malignancy, protein C/S deficiency
  - Work-up: DIC labs, blood cultures, skin bx w/ GS and culture. Tx: broad-spectrum abx + supportive care
- **Stasis dermatitis**: LE compression (ACE wraps, stockings) with elevation; mid-strength to super potent corticosteroid ointment BID x 1-2wks +/- occlusion with plastic wrap; mupirocin ointment BID x1-2wks to erosions; intensive moisturization (hydrated petrolatum); for hyperkeratosis can liberally apply ammonium lactate BID until improvement
- **Psoriasis**: depends severity; avoid PO steroids d/t post-tx flare. Short-term tx incl topical steroids, calcipotriene, intense moisturizing +/- occlusion w/ plastic wrap; Long-term tx incl phototherapy, acitretin, MTX, biologics w/ outpt derm f/u (JAAD 2011;65:137)
- **Seborrheic dermatitis**: Face: least potent to lower mid-strength topical steroid BID x 1wk and/or ketoconazole 2% cream BID x4wks, then 1-2x/wk; Alternative: pimecrolimus cream, tacrolimus 0.03 or 0.1% ointment. Scalp: ketoconazole 2% shampoo QHS
- **Tinea pedis**: "moccasin distribution"; apply topical imidazole (econazole 1% cream QD or clotrimazole 1% cream BID x 2-4 wks) or allylamine (terbinafine 1% cream BID x 2 wks) to entire foot and webbed spaces between toes. Predisposes to LE cellulitis

Allergic Contact Dermatitis	Calciphylaxis	Erythema Multiforme	HSV	Purpura fulminans

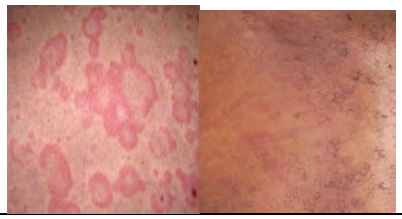
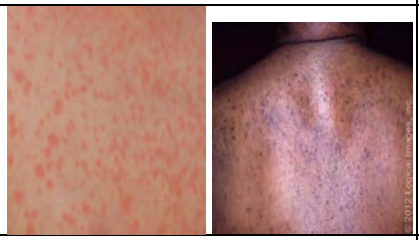
DRUG ERUPTIONS

- Step 1: Make timeline to determine time course of drug initiation and development of rash
- Step 2: **Discontinue** offending agent. Common drugs for each eruption listed, but **any** drug can be a culprit at **any** time

	Time Course	Rash	Signs/Sx	Common Drugs	Treatment

Consultants

Dermatology

Urticaria/ Anaphylaxis	Immediate (min-hr) – delayed (days)		Pruritic, well-circumscribed, erythematous papules/plaques with central pallor. **Transient** lesions (circle and observe) +/- angioedema, wheezing, GI sx, tachycardia, HoTN	Any	Antihistamines (benadryl + H2) + steroids if severe + IM epi if s/s anaphylaxis - Allergy c/s
Fixed Drug Eruption	Minutes-hours		Solitary sharply demarcated round red-brown patch or edematous plaque recurring in **same location** each time drug ingested. Can evolve to bullae/become disseminated. Oral/anogenital mucosa commonly, can be anywhere. Usually asx.	Abx (sulfa, TMP, FQs, TCNs), NSAIDs, barbiturates	Topical steroids if symptomatic
Acute Generalized Exanthematous Pustulosis (AGEP)	2-14 days		Small non-follic. pustules on erythema/edematous plaques, begin on face/intertriginous areas → widespread. Usually w/in 24-48hrs med exposure. Burning, pruritus common. Fever, marked neutrophilia +/- oral mucosal erosions, facial edema	Abx (PCN, macrolides)	Anti-pyretic Topical steroids
Exanthematous/ Morbilliform	4-14d (if prev. exposed to the drug, could be sooner)		"Classic" drug rash. Pruritic, erythematous macules/papules. Start on trunk, spread centrifugally to symmetric extremities. May lead to erythroderma. ± low grade fever	Abx (PCN, sulfa), allopurinol, phenytoin	Topical steroids, antihistamines (Note: may take 7-14d after stopping drug to resolve)
SJS/TEN	4-21 days		Fevers, malaise, myalgias, arthralgias. Pruritic atypical targetoid (amorphous, 2 color zones) macules→ bullae→ desquamation; <10% = SJS, 10-30% = SJS/TEN overlap, >30% = TEN. Mucosal bullae, erosions & crusting, conjunctivitis. + Nikolsky. Complications: 2° infection, resp. compromise, GIB, visual impairment	Abx (esp. sulfa), AED, NSAIDs, allopurinol, phenobarb.	Cyclosporine (preferred at MGH) Steroids possible mortality benefit (JAMA Derm 2017;153:514) but controversial IVIG, anti-TNF **Burn level care if >30% BSA Optho consult**
DRESS	3-6 wks		Morbilliform; spreads down symmetric. from face & mucosal involv. Face often swollen/painful (can help diff. from morbilliform drug) Fever, arthralgias, eos, internal organ involv. (liver, kidney; rarely lung, heart), LAD	Abx, AEDs, carbamazepine, ARTs (nevirapine, abacavir)	Dx: obtain CMP, CBC w/ diff, TSH, consider TTE - Supportive care - IV Solumedrol (decreased risk of bowel edema vs. PO), SLOW taper (3-6 wks), TSH check at 4-6 wks

Consultants Surgery

See *Calling Consults* for details on how to call the appropriate surgical service

SMALL BOWEL OBSTRUCTION (J Trauma Acute Care Surg 2015;79:661)

- Causes: adhesions from any previous abd surgery, hernias, cancer >> intussusception, volvulus, foreign bodies, stricture
- Dx: abd distension, nausea/vomiting, obstipation. Labs normal or hypoK/hypoCl metabolic alkalosis from repeated emesis. Examine for evidence of hernia and abdominal scars. If severe pain or peritoneal signs, consider ischemia from strangulation (lactate, WBC)
- Imaging: KUB – initial, air-fluid levels; **CT A/P w/ IV +/- PO contrast** (PO only if tolerated) – **best**, dilated bowel proximal to & decompressed bowel distal to obstruction. *Caution*: sending pt with SBO to CT w/o NGT = aspiration risk, empirically place prior to CT
  - SBO vs ileus: SBO - **transition point** between dilated & decompressed bowel; ileus - diffusely dilated loops w/o transition
- Tx: **strict NPO (no meds via NGT)**, large bore **NGT** (18Fr always) to continuous low suction; consider Gastrografin challenge (90 cc undiluted GG PO or via NGT; clamp NGT x 1 hr; KUB 6 hrs post). **Consider OR** if signs of bowel ischemia, s/p RNY gastric bypass (internal hernia), closed loop, or no improvement in 72 hrs. **All pts need strict I/O & IVF resuscitation, accounting for NGT output.**

BENIGN BILIARY DISEASE (Prim Care 2017:44(4):575-597), see *Biliary Disease*

- Indications for cholecystectomy (CCY): symptomatic cholelithiasis; cholecystitis; choledocholithiasis; cholangitis; gallstone pancreatitis; gallbladder polyps (>1cm or rapidly growing)
  - Post-cholecystectomy syndrome (PCS): abdominal pain, dyspepsia recurring/persisting after CCY; *early* (due to biliary injury, retained stones, retained cystic duct), *late* (due to recurrent CBD stones, strictures, stenosis, biliary dyskinesia), consider alternate non-biliary etiology (Int J Surg 2010;8:15)
- Acute cholecystitis: persistent RUQ pain + tenderness, cholelithiasis, caused by cystic duct obstruction. Dx: RUQUS – GB wall thickness >3mm, pericholecystic fluid, stones; **HIDA scan** – confirmatory test, non-visualization of gallbladder = positive.
  - Tx: IV abx (CTX/Flagyl or Zosyn), early CCY during hospitalization assoc. with ↓ morbidity (Br J Surg 2015;102:1302). If critically ill, perc chole → delayed CCY (at least 6 wks later).
- Gallstone pancreatitis: See *Pancreatitis*; findings include ↑lipase, ↑LFTs (↑ALT > 3.5x ULN, 95% PPV)
  - Consider Urgent ERCP (24 hrs) if cholangitis or CBD obstruction; same-admission CCY +/- IOC in mild cases associated with ↓ readmission for gallstone-related complications compared to delayed CCY (Br J Surg 2016; 103:1695)
- Acalculous cholecystitis: seen in critically ill ICU pts usually with prolonged NPO + biliary stasis, high mortality rate
  - Tx: perc chole + IV antibiotics
- Choledocholithiasis: CBD obstruction, jaundice. ↑AST,ALT (<1000), ↑ALP, ↑direct bili. RUQUS with CBD dilation, **MRCP**.
  - Tx: GI c/s for ERCP + surgery c/s for same-admission CCY. Can consider immediate CCY+IOC for select patients.
  - If concern for cholangitis (Charcot's triad – fever, RUQ pain, jaundice, Reynolds' pentad – + AMS, shock) → IV abx (Zosyn or CTX/Flagyl), IVF, close monitoring and **urgent ERCP**, same admission CCY. *Can cause rapid clinical decompensation*.

NECROTIZING SOFT TISSUE INFECTION (CID 2007;44:705; Front Surg 2014;1:36)

- Definition: progressive, rapidly spreading infection with secondary necrosis of skin and subcutaneous tissues, +/- fascia & muscle
- Microbiology: majority of cases are polymicrobial (anaerobes, group A strep, *S. Aureus, Clostridium*, *Peptostreptococcus*, *Enterobacteriaceae, Proteus*, *Pseudomonas*, *Klebsiella*)
- Clinical signs: **rapidly spreading erythema** (hrs to days) → pain disproportionate to exam or beyond borders of erythema, dusky skin, turbid ("dishwater") discharge, crepitus, bullae, fever, hypotension; Fournier's gangrene (perineum) & Ludwig angina (jaw/neck)
- Dx: **clinical dx**, **CT w/ IV contrast** has a ~95-100% NPV. Labs for **LRINEC** score (CRP, WBC, Hg, Na, Cr, Gluc) → score ≥6 has a 92% PPV & 96% NPV (Crit Care Med 2004; 32:1535-41). Bedside I&D if equivocal (dishwater fluid, loss of tissue integrity, malodor)
- Tx: **IV abx** ([Vanc or Linezolid] + [Pip/Tazo or meropenem] + Clinda (to inhibit toxin production) + **emergent surgical debridement (consult Churchill service immediately)**

ACUTE LIMB ISCHEMIA (NEJM 2012; 366:2198)

- Clinical signs: **6 P's: P**ain, **P**oikilothermia (cool), **P**aresthesia, **P**allor, **P**ulselessness, **P**aralysis
- Dx: check pulses & Doppler signals in both affected & unaffected extremities for comparison. Obtain ankle-brachial indices. CTA
  - **Acute limb ischemia** → acute decrease in limb perfusion 2/2 thrombosis or embolism (can be iatrogenic, e.g., s/p vascular access procedure), needs *urgent surgical evaluation*
  - **Chronic limb ischemia** → chronic vascular disease from atherosclerotic changes. Exam with cool, hairless extremities, limited/no pulse/absent Doppler signals that is not acutely painful (perfusion maintained by collaterals). *Non-urgent* surgical eval
- Tx: if unsure, or acute limb ischemia, IV heparin (unless AC contraindicated); **consult Vascular Surgery immediately**

COMPARTMENT SYNDROME (EXTREMITY) (Lancet 2015;386:1299; Musc Lig Tend J 2015;5:18)

- Definition: excessive pressure within a muscle compartment impairing perfusion; 2/2 crush injury, edema, bleed, ischemia, etc.
- Clinical signs: tight, tender skin; pain out of proportion to exam; **pain with passive ROM**; ↑lactate or CPK
- Dx: **clinical dx,** measurement of compartment pressures w/ Stryker transducer needle if equivocal (call Ortho or Churchill Service)
- Tx: surgical emergency (fasciotomy/decompression); **consult Churchill Surgery immediately**

ABDOMINAL COMPARTMENT SYNDROME (ICM 2013;39:1190)

- Definition: IAH = IAP ≥12. Abdominal Compartment Syndrome = IAP >20 AND end organ dysfunction (e.g.,↑airway pressures, ↓UOP/AKI, ↑lactate, acidemia). IAP measured via bladder pressure (most reliable if paralyzed, done in ICU)
- Typically occurs after massive resuscitation in ICU patients with trauma, burns, s/p liver txp, severe ascites, pancreatitis, sepsis
- Tx: for medically refractory, true Abdominal Compartment Syndrome → **decompressive laparotomy with temporary closure**
  - If IAP 12-20 w/o clinical instability, temporize w/NGT, rectal tube, paralysis, LVP, ↓tidal volume, diuresis, HOB elevation

Consultants Urology

Who to call: page 11300 for Emergencies, Foleys, SPTs, & gross hematuria; page 10300 for other non-urgent inpatient consults
Consults: note urine color **in tube** (bag urine appears darker due to volume) before consulting Urology, place urine samples at bedside – use food/drink comparisons like "pink lemonade," "fruit punch," "cranberry juice," and "merlot" to help characterize

URETERAL OBSTRUCTION (MOST COMMONLY DUE TO KIDNEY STONES OR MALIGNANCY)

- **Evaluation/management**: Pain usually present only in **obstructing** stones. +hydronephrosis implies obstruction.
  - Imaging: stone-protocol CT scan **(I⁻, O⁻)**: evaluates position, density/composition & presence of hydronephrosis
    - Alternative: MRI vs combined KUB+US; however, less diagnostic than stone-protocol CT. US helpful to r/o hydronephrosis
  - Vitals, CBC, UA/UCx: if concomitant UTI, decompress urgently with stent by urology or percutaneous nephrostomy (PCN) by IR
  - Rehydration: patients often volume down, bolus as tolerated and increase maintenance IV fluids → ↑ureteral clearance
  - Alpha-Blockers: **tamsulosin** 0.4mg PO qd (hold for SBP <90) → ureteral relaxation, +evidence for better **distal** stone passage
  - Analgesia: Tylenol, NSAIDs if Cr <1.5, add IV opioids if inadequate pain control; can also use diazepam (2mg Q8 PRN)
  - Preoperative workup: NPO, BMP/CBC, continue AC if plan for Urology stent; hold AC & obtain coags if plan for IR PCN
- **Urgent urology consults**: solitary or transplanted kidney with worsening AKI, UTI, urosepsis in setting of obstruction
- **Obstruction + sepsis**: Non-con CT A/P ASAP, BCx/UCx, urgent Urology consult; broad IV abx to cover GNRs + enterococcus
- **Non-stone hydronephrosis**: often stricture or malignancy, can require decompression for renoprotection or need for nephrotoxic chemo. Same options (stent vs PCN), same indications of urgent/emergent consult. Urology can help determine stent vs PCN
- *Relevant History:* renal colic is unilateral pain from CVA wrapping around flank radiating towards ipsilateral scrotum/labium
- **Indwelling ureteral stents:** Need exchange every 3-6 months; if +UCx, need abx treatment prior to exchange; can be done as outpt

HEMATURIA

- **DDx**: BPH, UTI, INR>3, traumatic catheter placement, bladder CA (5th most common neoplasm), upper urinary tract CA, prostate CA
- **Acute Management**: Obtain post-void residual bladder scan before consulting Urology. If +foley, can manually irrigate & and aspirate
  - **DO NOT start CBI if active clot burden. If 3-way clots off, stop CBI and manually irrigate through 3-way until clear**
  - Manual irrigation removes clots that already exist, while CBI prevents new clots from forming by diluting active bleeding
- **Diagnostic Workup** (4 C's): 1) in-house **CT hematuria protocol**; 2) urine **Culture**, 3) urine **Cytology**, 4) outpatient **Cystoscopy**

OBSTRUCTED CATHETER VS BLADDER SPASM/URGENCY FROM CATHETER

- **Obstructed Catheters**: bladder feels full, urine spasms around catheter, minimal/no urine through catheter, bladder scan is high
  - Tx: disconnect tube from drainage port, gently flush 50cc and aspirate with catheter-tip syringe and reconnect
- **Bladder Spasm**: bladder feels full, urine spasms around catheter but continued flow through catheter, bladder scan is low
  - Tx: antispasmodic agents – restart home meds if they have them normally, otherwise can start **tolterodine** (anticholinergic with fewer side effects than oxybutynin), Oxytrol patch and/or **belladonna-opium suppository** (local anticholinergic)
- *Note:* bladder scans are inaccurate when patients have ascites because they inappropriately detect the fluid around the bladder

URINARY RETENTION

- **Etiology**: BPH, UTI, constipation, neurogenic (MS, cord injury), DM, immobility, anticholinergics, opioids, benzos, pelvic surgery
- **Treatment**: **bowel regimen**, treat UTI, **minimize opioids/anticholinergics**, encourage **ambulation**, (re)start **tamsulosin** or other α-blocker. Catheterize as necessary – clean intermittent "**straight cath**", preferred long-term to Foley/SPT if possible

URINARY INCONTINENCE

- **Classifications**: stress (Valsalva), urge (preceded by urgency), mixed (most common), overflow (PVR >150), functional (neurologic)
- **Treatment**: lifestyle interventions, bladder training (timed voiding), Kegel pelvic floor exercises for all types
  - Stress: vaginal estrogen (post-menopausal women w/ vaginal atrophy), pessaries (mixed data), surgery (urethral bulking, slings)
  - Urge: antichol (oxybutynin, tolterodine, beware side effects), β3-agonists (mirabegron, avoid w/ HTN, ESRD, ESLD), Botox
- *Note:* workup of "voiding dysfunction" (retention, incontinence) usually takes weeks/months of outpatient observation ± urodynamics.

TUBES AND DRAINS: see *Tube Management* for placement and management

- **Foley catheter**: externally placed tube which travels through urethra and into bladder
  - Considerations: BPH, men >50yo → 16-18Fr Coudé (gentle curve directs catheter tip through curve of prostate), **all RNs are allowed to place Coudés – the tip (and balloon port) point "up" towards sky**; stricture → 12-14Fr
    - *Pro-tip:* use 8-10cc lubricant **instilled into the urethra** via syringe (urojet) for easier catheter placement in men
  - Urethral trauma: To avoid, fully hub foley on placement prior to balloon inflation; leave foley in 3-5d to allow for urethral healing
- **Suprapubic tubes (SPT)**: externally placed tube travels percutaneously through ant abdominal wall into bladder
  - Placed by IR. First exchange done by IR, change q6-12w similar to Foley, **RNs do routine exchange, Urology assists PRN**
- **Percutaneous nephrostomy tube (PCN)**: externally placed tube travels percutaneously through flank wall into renal pelvis
  - Placed by IR under local vs general anesthesia. Cannot be coagulopathic, thrombocytopenic, or on ASA/anticoag
  - Urine collects in external bag. If low UOP into bags, passage of blood or concern for malposition – flush>obtain US/CT>call IR
- **Ureteral stent**: internally placed tube travels from renal pelvis to bladder inside ureter to drain kidney into bladder
  - Placed by Urology in OR with general anesthesia or MAC, requires change every 3-6mo. May cause urinary urgency. NOT changed in setting of infection unless stent has failed (which becomes a ureteral obstruction c/b UTI, tx usually = PCN with IR)
- *Note:* if stents/PCNs/chronic catheter or SPT/ileal conduit or neobladder – UTIs diagnosed on symptoms over UCx/UA (colonized)
- *Note:* there are no good data that Foley/SPT exchange in UTI is helpful because the new tube goes into the same (infected) tract

Consultants ENT

EPISTAXIS (NOSEBLEED)

Acute management: (UpToDate Epistaxis)

1. Have patient **lean forward**, **pinch nostrils**, and hold **pressure for 20 min**
   - Guidance: pinch over the soft portion of the nose; do NOT lean head back or pinch bony part of nose; **do NOT "peek"** – hold continuous pressure for 20 min; patient may be unable to hold pinch, best for RN/MD to do
2. **Afrin (oxymetazoline 0.025%)** nasal spray (after gently clearing clots)
   - Guidance: **GENEROUSLY SPRAY (5-10 sprays) on both sides then hold pressure again for 20 min as above**
3. Control SBP (goal < 120) if much greater than baseline; correct coagulopathy if present and able to
4. **Consult ENT if continued bleed after above steps**
   - Treatment: silver nitrate cauterization, resorbable nasal packing, non-resorbable nasal packing, Neuro IR embolization
   - Non-resorbable nasal packing: risk of Toxic Shock very low; put patient on prophylactic cephalexin or clindamycin; packing typically removed after 5-7d (whether inpt or outpt – can be removed by anyone by pulling on string)

Location: most are anterior bleeds from Kiesselbach's plexus (90%); **posterior bleeds are more rare / serious / difficult to manage**

Hx: duration and frequency of bleeding; laterality; EBL; prior episodes (and txs); trauma (fingers, fists, foreign body, etc.); prior nasal surgery; PMHx or FHx of coagulopathy; medications (in particular **anticoagulation**); cocaine or intranasal drug use

Exam: rapidity of bleeding; inspect nasal septum and OP for originating site; **suction clots from OP to protect airway if rapid bleed**

Tests: CBC, PT, PTT, T&S (consider crossmatch pRBC if brisk bleed)

Epistaxis prevention: after resolution x 2 weeks: petroleum ointment; avoid nose blowing / digital manipulation / vigorous exercise; keep head above heart; sneeze w/ mouth open; humidification (saline nasal spray BID); Afrin / hold pressure PRN re-bleeding

STRIDOR

Acute management:

1. Administer oxygen (low flow = NC, simple face mask, non-rebreather; high flow = venturi mask, HFNC); ensure IV access
2. Racemic epinephrine neb x 1 STAT (lasts ~2h); 10mg dexamethasone IV x 1 STAT (re-dose q8h)
3. Consider Heliox, abx, and humidification; IM / IV epinephrine and Benadryl if allergy suspected (see *Angioedema & Anaphylaxis*)
4. **If unstable → RICU & trauma surgery (x6-3333) for possible surgical airway; if stable → ENT for airway evaluation**

Hx: timing/evolution; inspiratory / expiratory / biphasic; inciting events, prior episodes; evidence of infection; allergy; hx EtOH/tobacco (cancer risks); hx subglottic stenosis; hx of known cancer of head and neck or radiation

DDx (in adults): iatrogenic / post-intubation (laryngeal / vocal cord edema or praxis of the recurrent laryngeal nerve from ET tube); infectious (epiglottitis, laryngitis, laryngotracheitis [croup], bacterial tracheitis, Ludwig's angina); allergic / angioedema; mass of larynx or trachea; neurological (vocal cord spasm / immobility); foreign body; trauma

Imaging: if stable, CT with contrast of head / neck / chest to localize source

DEEP NECK SPACE INFECTION (see *Head & Neck Infections*)

Acute management: (UpToDate Deep Neck Infection):

1. **Ensure protected airway**: intubation or surgical airway for threatened airway → consider glucocorticoids
2. **Empiric antibiotics**: typically need **polymicrobial** coverage (ensure appropriate anaerobic coverage)
   - E.g., amp/sulbactam vs 3rd gen cephalosporin + flagyl; consider vancomycin in pt with risk of MRSA or if sinogenic source
   - Vancomycin/cefepime/flagyl if healthcare-associated, severe, or immunocompromised
3. **ENT consult for consideration of drainage** (localized infection) and airway monitoring

Symptoms: sore throat; **trismus (inability to open jaw);** dysphagia / odynophagia; dysphonia; dyspnea / stridor

Exam: neck tenderness; lymphadenopathy; trismus, fullness / asymmetry of OP; crepitus; pooled saliva; stridor

Tests: CBC, PT, PTT, T&S; blood cultures; CT neck with contrast; MRI neck with contrast if c/f osteo

Complications: based on location: *parapharyngeal*: involvement of carotid sheath (CCA, IJV, CN X), carotid blowout (life-threatening), jugular thrombophlebitis (Lemierre's); *retropharyngeal*: extension along deep neck spaces/mediastinum (mediastinitis / empyema); *prevertebral*: spine osteomyelitis; *submandibular/sublingual:* Ludwig's angina (floor of mouth swelling, rapid resp compromise)

ACUTE SINUSITIS (Otolaryngol Head Neck Surgy 2015;152:S2)

Definition: **up to 4 weeks of purulent nasal drainage + nasal obstruction or facial pain / pressure / fullness (or both)**; can be viral or bacterial (typically bacterial if symptoms > 10 days)

Symptoms: *uncomplicated* (confined to sinuses): facial pressure / pain, purulent nasal discharge, nasal obstruction, fever, malaise, anosmia, dental pain, ear fullness; complicated (extra-sinus extension): vision changes, proptosis, mental status changes, severe HA, facial soft tissue changes; in immunocompromised/critically ill: consider **invasive fungal sinusitis, a surgical emergency** (see *Invasive Fungal Infections*)

Workup: *uncomplicated*: no imaging required; *complicated*: CT w/ contrast ± nasal endoscopy to look for evidence of purulence

- If concern for invasive fungal sinusitis, consult ENT for consideration of nasal biopsy with STAT pathology

Treatment:

- Uncomplicated ABRS: amoxicillin ± clavulanate 5-10 days; nasal steroid spray / nasal saline irrigations for symptomatic relief; if no improvement after 7 days change antibiotic
- Invasive fungal sinusitis: **liposomal amphotericin**, urgent surgical debridement, ID consultation

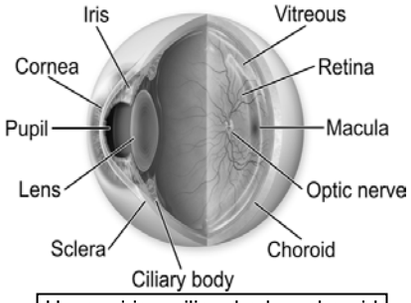
SUDDEN HEARING LOSS (Otolaryngol Head Neck Surg 2019;161:S1)

1. Use otoscope to examine ears and **ensure no cerumen impaction**
2. Determine conductive hearing loss vs sensorineural hearing loss – obtain **audiogram**, call 617-573-3266 at MEE to schedule
3. If sensorineural hearing loss, consult ENT for initiation of either high dose oral corticosteroids or intra-tympanic steroids if contraindication to systemic steroids; ideally start steroids within 2 weeks of symptom onset

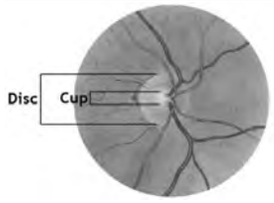
Consultants Ophthalmology

Ask PMH abnl vision, eye sx, meds, cataract, glaucoma, macular degen, DM retinopathy, and do basic eye exam *prior* to consult!

General inpatient consult: **check paging directory and page/call listed number;** can also call MEEI ED desk **617-573-4063**



Uvea = iris + ciliary body + choroid



Basic Eye Exam: "Ocular Vital Signs"

- Visual Acuity (e.g. 20/200, CF)
- Pupils (4mm → 2mm OD, No APD)
- Confrontational visual fields
- Extra-ocular movements
- Intraocular pressure (nl 10-20mmHg)
- Color vision testing (Ishihara cards)

Common Abbreviations:

APD	Afferent pupillary defect	NLP	No light perception (VA)
AT	Artificial tears	NPDR	Non-prolif. diabetic retinopathy
cc/sc	With/without correction (glasses)	NS	Nuclear sclerosis (i.e. cataract)
CE	Cataract extraction	OD/OS	Right eye, left eye
CF	Count fingers (VA)	OU	Both eyes
CWS	Cotton wool spot	PDR	Proliferative diabetic retinopathy
DES	Dry eye syndrome	PF	Pred Forte gtt (prednisolone)
DFE	Dilated Fundal Exam	PFAT	Preservative-free artificial tears
EOM	Extraocular movement	PH	Pinhole acuity
HM	Hand motion (VA)	PVD	Posterior vitreous detachment
IOL	Intraocular lens	RD	Retinal detachment
IOP	Intraocular pressure	SLE	Slit lamp exam
LP	Light perception (VA)	SPK	Superficial punctate keratitis/dry eye
MGD	Meibomian gland dysfunction	VA, VF	Visual acuity, visual fields

High-Yield Pearls

- **Vision loss**: acute (requires urgent evaluation) vs chronic (outpt referral) – assess patient with their glasses on!
- **Glaucoma drops**: prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors, or alpha 2 agonists – all lower IOP
  - *If brand-name drops unavailable:* fractionate combo meds, ask pharm for substitution advice, or have pt bring in home meds
- **Dilating drops**: 0.5% tropicamide (parasympathetic antagonist), 1-2 drops placed 15-20 minutes before exam; light-sensitive 4 hours
- **Finding the retina:** dilate the eye and use the ophthalmoscope; see example Stanford Medicine fundoscopic exam video

Common Eye Pathology

- **Red Eye**: typically benign; refer to ophtho if no improvement or **any "ocular vital sign" changes** (see above)
  - **Viral conjunctivitis**: eyes "stuck shut" in AM, itchy, crusty discharge, ± URI symptoms, ± pre-auricular nodes, winter time
    - Tx: supportive/isolation (typically adenovirus, highly infectious). Wash hands thoroughly if you suspect this!
  - **Allergic conjunctivitis**: olopatadine 0.1% gtt bid x 5d. Clear Eyes/Visine not rec'd (rebound redness 2/2 alpha agonism)
  - **Anterior uveitis**: pain and true photophobia ± eye injection. Usually perilimbal. Hx autoimmune ds common. **Refer to MEEI ED**
  - **Contact lens keratitis**: pts remove contacts on admit! P/w red/painful eye; infection until proven otherwise. **Refer to MEEI ED**
  - **Acute angle closure glaucoma**: common sx include nausea, aching pain, vision loss. Palpation of the eye will be "rock hard" or elevated pressure with tonopen. Exam: red eye, hazy cornea, mid-dilated pupil. **Urgent consult to MEEI.**
  - **Subconjunctival hemorrhage**: blood between conjunctiva and sclera from ruptured vessel. No vision changes, not painful. Can be 2/2 blood dyscrasia, Valsalva (cough, vomit), trauma, AC, spont. Resolves spont. No need to consult if no significant trauma.
- **Blepharitis** (inflammation of eyelids): p/w crusting, red eye, gritty feeling
  - Tx: baby shampoo, warm compresses, abx ointments x 2 weeks, then daily lid hygiene. Tx for **hordeolum ("stye")** is same
- **Dry Eye Syndrome (DES)**: p/w eye pain or "grit"/paradoxical tearing ± vague "blurriness"
  - Tx: preservative-free artificial tears (Refresh) q1h prn , Refer to ophtho if no improvement. Approach to blurry vision
- Corneal abrasion/exposure keratopathy: unilateral, redness, mild light sensitivity, common after sedation
  - PPx: intubated patients require lubrication regimen (ophthalmic lubricating ointment QID) ± tape eyelids shut if partially open
  - Dx: apply fluorescein (order in Epic) to the affected eye, illuminate with a blue light (e.g. ophthalmoscope, smartphone screen with Eye Handbook App). Abrasion will light up green; keratopathy will look like "sandpaper" instead of smooth glass
  - Tx: abx ointment (Erythromycin 0.5%/bacitracin ophthalmic QID) + Lacrilube qhs. Consult if no improvement after 24h
- **Anisocoria (unequal pupils)**: old (20% population has at baseline) vs. new (can be trivial 2/2 anticholinergic vs. catastrophic from herniation). Always ask for **h/o ocular surgery** as surgical pupil is a common benign cause

Miosis (Constricted Pupil)	Mydriasis (Dilated Pupil)
↑*Cholinergic* (e.g. morphine, pilocarpine)	↑*Sympathetic* (e.g. atropine, CNIII paralysis)
↓*Sympathetic* (e.g. Horner's)	↓*Cholinergic* (e.g. epinephrine, cocaine)

  - If clinical suspicion for herniation (known bleed, CN3 palsy, obtundation, hemiparesis) → **STAT head CT**
  - **Horner's Syndrome**: ptosis, miosis, ± anhidrosis. Wide ddx along pathway from posterior hypothalamus → C8-T2 → superior cervical ganglion → sympathetic chain → internal carotid → orbit. Head and neck CTA/MRA to r/o carotid dissection
- **Retinal detachment**: presents with flashes/floaters/curtain coming over vision. Risk factors: myopia (near-sighted), trauma, diabetic retinopathy, prior eye surgery. Tx: **Refer to MEEI ED** for likely vitreoretinal surgery. Approach to flashes, floaters, spots
- **Orbital Cellulitis** (see Orbital & Preseptal Cellulitis): most common from sinus disease, periocular edema/erythema + orbital signs (rAPD, color vision loss, motility disturbance, proptosis). Non-con CT face and orbits for stranding/abscess. **Consult MEEI**, likely needs admission for IV abx. **Preseptal** negative orbital signs, negative scan, can treat with oral abx and reassess symptoms.
- **Endophthalmitis**: infection within globe. Can be 2/2 trauma, surgery, or endogenous source (bacteremia/fungemia)
  - Tx: **ophtho c/s**, antibiotics/antifungals that will penetrate blood-brain barrier. May require vitrectomy (surgery)
- **Optic neuritis**: p/w painful EOM, subacute blurry vision (typically monocular), central scotoma. Causes: demyelinating ds (MS), infection, autoimmune (sarcoid, lupus). Tx: HD steroids; c/s ophtho/neuro. Approach to double vision

Huey Shih

Consultants OB/GYN

How to Consult

- **Obstetrics/MFM**: For inpatient consults for patients with a known intrauterine pregnancy, page the MFM team (p17977)
  - If no response, call L&D 617-724-9410
- **GYN Onc**: if pt has biopsy confirmed GYN malignancy or established GYN onc provider (p31037)
- **GYN**: Everyone else (e.g., +hCG without confirmed intrauterine pregnancy, undifferentiated ovarian mass, heavy vaginal bleeding).

  Obtain pelvic vs. transvaginal **U/S**. If hCG⊕ but no confirmed intrauterine pregnancy on imaging, should be followed on **ectopic list** (p22346)

Abnormal Uterine Bleeding

- **History**: verify source of bleeding is vaginal (as opposed to GI or GU), duration and quantity (#soaked pads, tampons), associated sx (pain, dizziness), triggers (e.g., postcoital), trauma history. Other history: estrogen contraindications (smoking, BMI, HTN, h/o coagulopathy), LMP/menstrual hx, full pregnancy hx, known GYN conditions (e.g., fibroids), meds (hormones, AC)
  - **Heavy bleeding** = **soaking through 1 pad per hour**, symptomatic, Δ VS, ↓Hgb
- **Exam**: external vulvar exam, speculum exam (note how many scopettes required to clear bleeding, volume of blood in vault, cervical lacerations, blood actively coming from cervix). Do NOT do digital exam if pregnant.
- Postmenopausal bleeding is never normal and often warrants a workup to rule out malignancy. If premenopausal, rule out pregnancy and its complications.

Differential Diagnosis for Abnormal Uterine Bleeding	
Pregnant	**Ectopic pregnancy**, miscarriage (including incomplete and septic abortion), subchorionic hematoma, placental abruption, placenta previa/accreta, vasa previa, trophoblastic disease, cervical/vaginal/uterine pathology (e.g. polyp)
Not pregnant	PALM-COEIN: Endometrial/cervical polyp, adenomyosis, leiomyoma/fibroids, **malignancy** (e.g., endometrial, cervical), coagulopathy, ovulatory dysfunction, endometrial dysfunction, iatrogenic, not otherwise classified (thyroid disease, vaginal/vulvar etiologies [e.g., laceration, atrophy]).

- **Workup**: CBC, T&S, coags, pad count (Epic order, monitors bleeding quantity)
  - If premenopausal, first step is **urine hCG**
    - If ⊕, obtain **serum quant hCG** and **pelvic U/S** (must **rule out ectopic pregnancy** in all pregnant women with bleeding)
    - If intrauterine pregnancy not confirmed on U/S, measure serial **serum hCG q48h** (should increase 35-50% in 48h) and repeat pelvic U/S. Ectopic risk factors: IVF pregnancy, h/o STIs, prior ectopic, h/o tubal surgery, IUD, smoking
  - If postmenopausal, **pelvic U/S**, consider endometrial biopsy if endometrial lining >4mm (difficult to do inpatient) *Regardless of U/S result, postmenopausal bleeding warrants at least outpatient GYN follow up*

Pelvic Pain

- **History**: timeline, severity, LMP, associated sx (N/V, GI, GU, fevers/chills, vag bleeding/discharge, wt loss), pain med requirement
- **Exam**: abdominal, CVA tenderness, bimanual exam, consider speculum exam if bleeding or discharge
- **Differential Diagnosis**: non-exhaustive list of most common causes of pelvic pain
  - **Ectopic**: see above; if peritoneal signs on exam or hemodynamically unstable, consider ruptured ectopic **(surgical emergency)**
  - **Adnexal lesions**: benign (simple, hemorrhagic, dermoid, etc) vs malignant. If high c/f malignancy, obtain CA-125, CA19-9, CEA
  - **Ovarian torsion**: clinical dx, most predicted by acute unilateral pain (<8hr), vomiting, mass (>5cm) (HuRepro 2010;25:2276)
  - **PID**: ascending (e.g., STI) vs descending (e.g., diverticulitis); fevers/chills, vaginal discharge, CMT; complications include TOA
  - **Endometriosis/chronic**: dysmenorrhea, dyspareunia, dyschezia; r/o acute causes, consider outpatient follow up
  - **Non-GYN**: nephrolithiasis, UTI/pyelo, appendicitis, diverticulitis, constipation
- **Workup**: hCG, pelvic U/S, GC/CT, CBC with diff, UA/UCx; consider alternative abdominal imaging pending H&P (e.g., CTAP)

Pregnancy and Its Complications

Gravida/para (GP), G= #pregnancies, P= #births; TPAL (T=term births, P=preterm births, A=abortions, L=living children)

- Hypertensive complications: BP ≥140/90 is abnormal, **any BP ≥160/110 is an OB emergency**
  - **Differential**: chronic HTN (HTN <20w), gestational HTN (HTN >20w), pre-eclampsia (new HTN + proteinuria or new HTN ≥160/110), pre-eclampsia with severe features (unrelenting HA, vision changes, RUQ/epigastric pain, lab abnormalities), eclampsia (seizure), HELLP
  - **Workup**: CBC, BMP, LFTs, LDH, uric acid, urine protein/Cr ratio +/- coags and hemolysis workup
- Hyperemesis: standing meds most effective, see tx algorithm on UTD
- OUD/SUD: can refer to HOPE Clinic.
- References: Normal lab values by trimester (UTD). Guide to OTC med use/symptom tx during pregnancy: AFP 2014;90:548

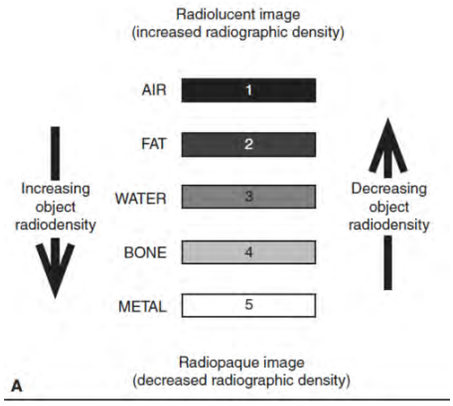
Radiology

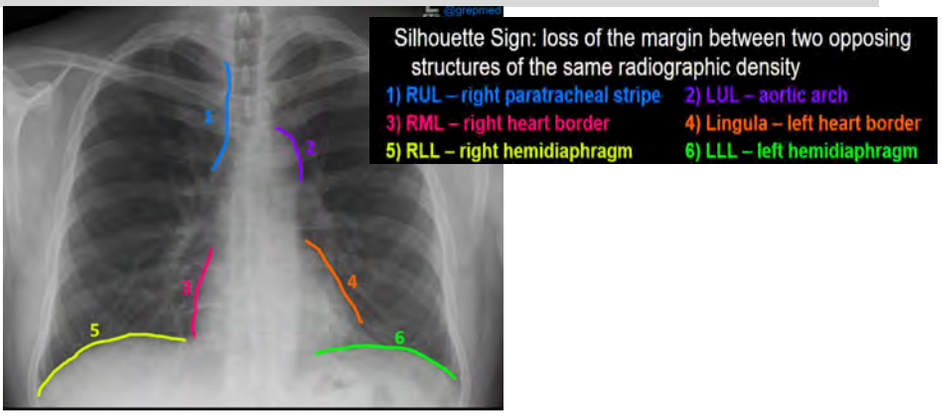
Radiology Basics

Imaging Orders

Always include *brief* clinically relevant information to inform the radiologist of your clinical question.
Think of the radiologist as a **consultant** with the goal of adding valuable diagnostic information to patient care via imaging.

X-ray



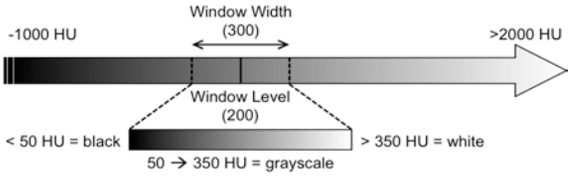

Silhouette Sign: loss of the margin between two opposing structures of the same radiographic density
1) RUL – right paratracheal stripe
2) LUL – aortic arch
3) RML – right heart border
4) Lingula – left heart border
5) RLL – right hemidiaphragm
6) LLL – left hemidiaphragm

Computed Tomography (CT)

Hounsfield Units (HU): measurement of CT attenuation (see table for reference range)
Windowing: adjusting contrast (width) and brightness (level) to better visualize specific structures.

- Window width ("contrast" - *range* of grayscale): range of Hounsfield units. HU < window = black, HU > window = white, within window = gray. Wide windows for large diff in density (i.e. air/vessel in lung), narrow for similar density (grey vs white matter)
- Window Level ("brightness" - *center* of grayscale): HU at center of window, corresponds to attenuation of structure of interest (e.g. high lvl for bone window, low lvl for lung window)

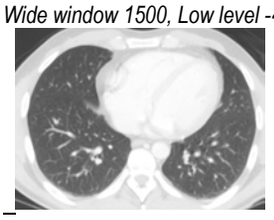
Phase	Time Post-Injection	Structures Evaluated
CT-PE	5-15 s	Pulmonary arteries
Arterial (CTA)	15-20 s	Systemic arteries, no organs
Late arterial	35-40 s	Arteries, renal corticomedullary differentiation
Late Portal	70-80 s	Organs (Routine abdomen)
Nephrographic	100 s	Renal parenchyma
Delayed (Vascular)	120 s	Active contrast extravasation (bleeding), peripheral veins
Delayed (Urogram)	10-15 min	Ureters, bladder



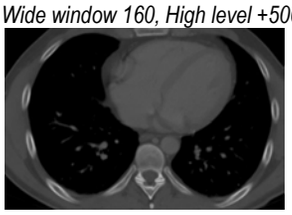
"Bone Window"

Substance	HU
Air	-1000
Fat	-100
Water	0
Blood	50
Soft tissue	100
Bone	1000
Metal	>2000

"Lung Window"
"Brain/Soft Tissue Window"
Wide window 1500, Low level -40



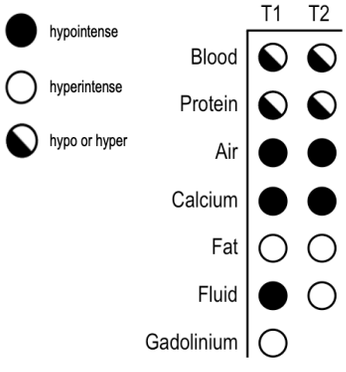
Wide window 160, High level +500;



Narrow window 80, Medium level +40

Magnetic Resonance Imaging (MRI)

MRI safety: search device compatibility at mrisafety.com



Basics of Common MRI Sequences	
Sequence	**Purpose**
T2 weighted +/- fat-sat	Identify fluid/edema (e.g. most pathology, malignancy). Fat sat refers to technique to make fat appear hypointense.
T1 weighted +/- contrast	Evaluate anatomy; identify T1 hyperintense products, including hemorrhage, fat, protein & contrast (gadolinium) enhancement.
STIR	T2W (fluid/edema) with technique to make fat appear hypointense (more consistent than fat-sat). Common in MSK MRIs.
MRCP	Heavily T2W sequence to eval gallbladder + intrahepatic, extrahepatic, and pancreatic ducts.
HASTE/SSFSE	T2W sequence that is rapidly acquired (fast sequence).
GRE	ID hypointense susc (blooming) artifact a/w blood & calcium.
SPACE	High resolution 3-D sequence (cor, sag, axial).
DWI	Identify restricted motion of intra-/extracellular water molecules (e.g. acute stroke, abscess, highly cellular tumors like lymphoma).

Radiology — Contrast

Indications for CT Contrast Administration

- IV positive (**I+**): vast majority of studies more sensitive when given, particularly for **infection, tumors, and vessel imaging**
- IV negative (**I-**): urinary tract stones, retroperitoneal hematoma, pulmonary nodule follow-up
- PO positive (**O+**): bowel obstruction, bowel leak/perforation/fistula, differentiate bowel from other abdominal structures
- PO negative (**O-**): inflammatory bowel disease, GI bleed, mesenteric ischemia, retroperitoneal hematoma

Pregnancy and Breastfeeding (ACR 2022 Manual)

- Contrast Use in Pregnancy:
  - *Iodinated contrast for CT studies*: no need to withhold (no data to suggest potential harm to fetus, although limited data)
  - *Gadolinium contrast for MRI studies*: do not use unless essential + no suitable alternative (radiology consultation). Req consent.
  - Written consent required if predicted fetal dose >0.05mGy. 1 CT = ~25mGy to fetus. No consent for CXR, C/T-spine, mammo
- Breastfeeding: Current rec: I & G* safe for mother & infant, may choose to "pump and dump" for 24h after scan.
  - ***Exception – EOVIST**: unknown if Eovist excreted in milk. Consider "pump & dump", but likely safe to nurse after 10h

Renal Function (ACR 2022 Manual; MGPO 2020 (CIN); MGPO 2020 (NSF); JAMA IM 2020;2:223)

	Contrast Induced Nephropathy / Post Contrast Acute Kidney Injury (PC-AKI)	Nephrogenic Systemic Fibrosis (NSF)
Definition	• Association between intravenous / intra-arterial contrast and development of renal impairment • Occurs 48-72 hours after contrast admin	• Association b/w Gad-based contrast (MRI) in pts with renal impairment & development of systemic fibrosis • Occurs weeks to months after contrast admin
Risk factors	• **CKD (consensus most important)** • Diuretic use • > 2x contrast doses in <24 hrs • Diabetes mellitus • Dehydration • Cardiovascular disease • Age >60 years • Hyperuricemia	• 3 classes of contrast based on risk: I (highest risk), II (minimal risk), III (likely very low risk but limited data) • Some risk with Group I and III (e.g., **Eovist**) in patients with **kidney disease** (acute or chronic) and/or **DM**. • Risk "sufficiently low or possibly non-existent" w/ default Group II GBCAs (e.g. **Dotarem, Multihance**)
Screening	**Screen if h/o kidney dz or diabetes mellitus** Outpatient: eGFR within 30d, ED: eGFR within 30d, Inpatient: eGFR within 24h	Outpatient: not necessary for most scans Inpatient/ED: eGFR within 24hr for class III agent (e.g. Eovist). None needed for class II agent
Prevention	**eGFR ≥30: contrast per protocol (NO prehydration)** **eGFR <30 or AKI** → I- or alternative study. Consult radiology if I+ is medically urgent. Consider prehydration. Dose reduction not considered effective prevention	**Group II GBCA:** given regardless of eGFR **Group I GBCA:** consult radiology if eGFR <30 **Group III GBCA**: do *not* give if eGFR <30
On Dialysis	If maintenance dialysis **w/o possible renal recovery**: administer contrast. If **possible renal function recovery,** (e.g temporary dialysis catheter): consult radiology	**Consult radiology. Typically Gad withheld.** Prompt post-scan HD suggested (PD inadequate)
<24h repeat studies	Decision is clinical and subjective Insufficient evidence to hold contrast for 24h	No risk factors: proceed At risk patients: consult radiology
Metformin	eGFR ≥30: continue metformin eGFR <30 or AKI: hold for 48h after scan	Continue metformin
Renal txplt	Consult Radiology	Consult Radiology

***Post contrast peak effect on creatinine occurs 48-72 hours after administration**

Pre-hydration protocol: (ACR 2022) ***If you want an I+ CT scan in a patient w/ eGFR <30, speak to radiology**

- Prophylaxis indications: **eGFR <30** (not on long-term HD), **AKI**
- PO hydration: Not well-studied. Historical MGH regimen: 1-2L PO non-caffeinated beverage 12-24h prior to scan
- IV hydration: *Start 1 hr prior & cont 3-12 hrs after. Fixed volume (250-500 mL NS) before & after **vs.** weight-based (1-3 mL/kg/hr)*
- N-acetylcysteine is **NOT** recommended for IV contrast prophylaxis

Contrast Reactions (ACR 2022)

	Mild	Moderate	Severe
Allergic	Limited urticaria Itchy throat, congestion URI symptoms	Diffuse urticaria Facial/laryngeal edema w/o dyspnea or hoarseness Bronchospasm w/o hypoxia	Anaphylaxis Facial/laryngeal edema w/ dyspnea or hoarseness Bronchospasm w/ hypoxia
Physiologic	N/V, flushing/warmth HA/dizziness Mild HTN Transient vasovagal rxn	Protracted N/V HTN urgency Isolated Chest Pain Vasovagal rxn requiring tx	HTN emergency Arrhythmia Seizure Protracted vasovagal rxn

Indications for Premedication
• Prior mild-moderate allergic reaction • Prior unknown contrast reaction • None for prior physiologic reactions • None for shellfish allergies • **No** cross-reactivity b/w iodinated contrast and gadolinium

Standard contrast allergy pre-medication regimen: **13h**

- You *must* indicate standard premedication regimen in the imaging order
- Epic orderset – "Contrast Allergy Prophylaxis: Regular Protocol Order Panel"

- Urgent contrast allergy pre-medication regimen: **4h**
  - Requires discussion with a radiologist before starting regimen
  - Epic orderset – "Contrast Allergy Prophylaxis: Urgent Protocol Order Panel"
- See *Drugs and Contrast* section on pre-medication prior to scan

Radiology Protocols

ORDERING STUDIES

- **All cross-sectional studies are protocoled by radiology** – simply provide the necessary information:
  - Body part: Head, abdomen only, abdomen and pelvis, etc.
  - Modality: Ultrasound, Radiograph, CT, MRI, Fluoroscopy, PET whole body, PET Brain, HIDA Scan, etc.
  - Indication: clinical history relevant to the study
  - Contrast: "per radiology discretion" unless *specific* reason otherwise **(I+ IV; O+ oral; R+ rectal)**
  - Contraindications for contrast: renal transplant, kidney injury or prior allergic reaction (see *Contrast*)
  - Questions? - call the appropriate division or page the appropriate on-call radiologist (see *MGH Directory*)
    - Inpatient study questions? - call ED reading room **after 7PM weekdays/5PM on weekends** (unless STAT study). Otherwise, call divisions during work hours (8am-7pm weekdays/8am-5pm on weekends; vascular 8am-noon weekend).
- **Level of Urgency**:
  - Routine: order of interpretation depends on acquisition time
  - Urgent: takes priority over routine studies (performed within 6 hours)
  - STAT: **means NOW, high acuity/life threatening emergencies (i.e., trauma patient may be removed from the scanner for your patient);** these studies are typically (not always) performed in White 1 (ED scanners)
    - Must call the body or neuro ED radiologist for approval (MGH Directory)
    - Patient must be ready for immediate transport. Responding team must transport patient (no transport provided)
    - Patient must be accompanied by a responding clinician (≥PGY-2) capable of providing emergency care
    - Responding clinician must be present for the entire exam
    - Radiology will provide preliminary read: phone call for XR/US, at the scanner for cross-sectionals

OVERNIGHT READS BODY EXT.4-1533 | NEURO EXT.6-8188

- Full interpretation reads overnight: All ED studies
- Preliminary interpretation reads overnight (labeled "Imaging Note" found under the Imaging tab in Epic):
  - All acute CT-PE studies (inpatient and ICU)
  - **By verbal request**: inpatient and ICU studies
    - **Routine/Urgent ICU & inpt studies** only reviewed overnight if **urgent clinical question**. Consider face-to-face c/s in ED.
    - **STAT ICU and inpatient studies will receive a prelim interpretation.**
  - After communication with the primary team, all verbalized prelim reads for ultrasound and cross-sectional studies (CT/MRI) will be documented in the chart. Verbalized prelim reads for radiographs (XR) will be documented as needed.
  - All inpatient and ICU full interpretations will be generated the following morning by appropriate division

ED PROTOCOLS BODY X4-1533 | NEURO X6-8188

- Trauma: I+ (IV contrast), single phase (combo of arterial/portal venous – images checked at scanner by rads to decide if need delays)
  - Blunt trauma: includes bone kernel reformats for better visualization of bones; +/- Delays for parenchymal bleed
  - Penetrating trauma: O+R+ (Oral contrast, rectal contrast) for increased sensitivity of bowel injury
  - CT Cystogram: retrograde filling of bladder with contrast via Foley catheter to evaluate for bladder rupture
- Cervical spine: I-, need for follow-up CTA head/neck determined by radiology, bone kernel reformats in all 3 planes
  - Images checked at the scanner by radiology only if IV contrast is required for another body part
- Appendicitis: I+, possibly O+ or R+ (if GI contrast requested, please specify PO or PR), image kidneys through pelvis only
- Retroperitoneal Bleed: I-,O-
- Indications for MRI in the ED: Pediatric appendicitis after equivocal ultrasound || Appendicitis suspected in pregnancy || Rule out occult fracture || Osteomyelitis || Choledocholithiasis (MRCP)
- OB Ultrasound Studies: Covered up until 14 weeks

ABDOMINAL PROTOCOLS X6-5162

- Stone protocol: I-O-, low dose, prone
  - Order contrast-enhanced (I+) CT if there is c/f ANYTHING else (e.g. pyelonephritis) as stones likely still visualized
- Retroperitoneal hemorrhage: Routine abdomen/pelvis I-O-
- Routine abdomen/pelvis vs renal mass vs bladder cancer vs hematuria:
  - Routine abdomen/pelvis: I+O+, single phase (portal venous) → workhorse protocol
  - Renal mass: I+O+, two phases (noncontrast, nephrographic), abdomen only → renal masses or cysts
  - Bladder cancer: I+O+, two phases (portal venous, delayed) → workup or monitoring of GU malignancy
  - Hematuria: I+O-, "three" phases (noncontrast, nephrographic, urogram) → hematuria, hydronephrosis
- CT urogram vs CT cystogram:
  - Urogram: antegrade filling of ureters and bladder via excretion of IV contrast (delayed phase)
  - Cystogram: retrograde filling of bladder with contrast via Foley catheter to evaluate for bladder rupture
- Arterially-enhancing tumors: add arterial phase along to usual CT protocol
  - MR CHIT: **M**elanoma, **R**CC, **C**horiocarcinoma, **H**CC, **I**slet cell (neuroendocrine) tumors, **T**hyroid
- Time to be NPO: IV contrast CT: 2h || Abdomen/pelvis CT: 8h. || Non-contrast CT: no NPO
- Fluoroscopy protocols:
  - Requisition: specify indication, h/o surgery or aspiration
  - Barium swallow vs modified barium swallow vs UGI series vs SB follow-through:
    - Barium swallow: eval esophagus, GE junction, proximal stomach → dysphagia, GERD
    - Modified barium swallow: eval mouth, pharynx, upper esophagus → dysphagia, **aspiration**

- UGI series: barium swallow plus stomach, pylorus, and duodenal bulb → bariatric surgery pre-op eval
- SB follow-through: small bowel, terminal ileum, and proximal LB ± UGI series beforehand

CARDIOVASCULAR PROTOCOLS VASC X4-7115 | CARD CT X4-7132 | CARD MR X3-4457

- DVT imaging:
  - Compression ultrasound is the best initial test of choice (ACR 2018); Epic order "LENI" (**L**ower **E**xtremity **N**on-**I**nvasive)
  - CTV/MRV: primarily used for central venous thrombosis when initial US is equivocal or non-diagnostic
- Arterial imaging:
  - CTA: three phases (noncontrast, arterial, venous delays) → stenosis, dissection, aneurysm, active bleeding, systemic embolism/thrombosis (**not pulmonary embolism)**
  - Requisition: specify vessel of interest, field of view, and indication
- Coronary CTA:
  - ECG-gated study of the coronary vessels → only performed by cardiovascular CT
    - Requires beta blocker and vasodilator administration
    - **Not performed after 7pm on weeknights or noontime on weekends**, as cardiac techs are typically not in house
    - On call Cardiac CT Fellow is available for urgent questions after hours: p22122
  - Specify if body parts other than the heart should be imaged (thoracic aorta, CABG grafts, etc.)
- Other ECG-gated CTAs:
  - Indications: any eval of the heart or ascending aorta. ECG-gating unnecessary for descending thoracic/abd aorta & pulm arteries
- Noncontrast vascular studies:
  - Indications: Retroperitoneal hematoma, pre-op aortic calcifications, coronary calcium score, follow-up aortic size

THORACIC PROTOCOLS X3-3899

- All chest CTs are high resolution
- Routine chest vs CT-PE vs CTA chest:
  - Routine chest: single phase (late arterial) → workhorse protocol (read by Thoracic)
  - CT PE: single phase (pulmonary arterial) → **pulmonary** arteries (read by **Thoracic**), prelim by ED during off-hours
  - CTA chest: three phases (non-contrast, arterial, delays) → **systemic** arteries (e.g. aorta) (read by **Vascular**)
- Double rule out studies: (Clinical concern for PE and aortic dissection)
  - Contrast can only be optimized for one (must pick CT-PE or CTA)
- Diffuse lung disease (a.k.a. misnomer "high res CT"):
  - Indications: ILD, lung transplant, air trapping, bronchiectasis
  - Phases: Inspiratory and expiratory images, plus prone images to differentiate between atelectasis and fibrosis
- Nodule follow-up: (Radiology 2017;284:228; Please refer to Fleischner guidelines)
  - Indications: incidental nodule on prior CT, age >35y, **AND** no hx immune compromise, malignancy or recent infection
- Dual energy esophageal leak (I+/I-): Esophageal perf, postop leak; Tracheal Protocol: Tracheal stenosis, mass, stent

NEURORADIOLOGY PROTOCOLS

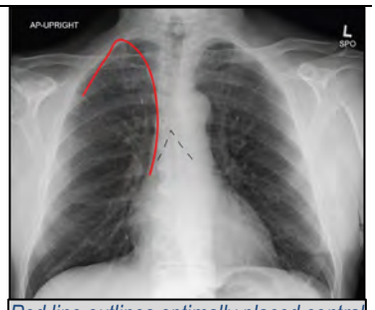
- Inpatients: page Neuro IP on-call radiologist at p32535
- Inpatients/ICU Acute Stroke: call x6-3333 & page p21723 acute stroke consult fellow (ED: activated ED2CT group pager)
- Head CT: typically noncontrast
  - Indications for contrast-enhanced head CT: infection and/or tumor AND contraindication for brain MRI
- Spine MRI: for more than one segment, **please order total spine** and specify indication
  - Separate MRIs should not be ordered prior to neurology/NSGY consult
- Fluoroscopy-guided LPs: performed by neuroradiology fellows, NOT neuro IR
  - Indications: difficult anatomy, and only after LP is attempted on floor
  - Typically performed without conscious sedation, although this can be arranged if required for patient safety

NUCLEAR MEDICINE PROTOCOLS NON-PET X6-1404 | PET X6-6737

- Tagged RBC study: BRBPR (**NOT** guaiac positive stools, melena, or massive bleeding)
  - Requirements: consult **IR BEFORE STUDY** to confirm angiogram will be performed if study is positive
- VQ scan: acute PE (NOT chronic PE), can happen overnight if results will alter management (i.e., AC tonight)
  - Technically just a perfusion (Q) scan since COVID; Ventilation (V) portion of the study is no longer performed.
  - Requirements: CXR or I- CT chest within 24h, patient stable and can tolerate laying supine for duration of scan (~4h)
- HIDA scan: acute cholecystitis
  - Requirements: NPO 4h prior to study, no opiates 12-24h prior to study, bilirubin <10, pt will need to tolerate lying supine
- PET: must be fasting, hold everything but meds and water (NO glucose containing fluids either ex: D5W)
  - Overnight is ideal for NPO, but at least 6h for non-DM patients
  - At least 4h for DM patients
    - Continue long-acting insulin, hold short-acting insulin 4h prior to scan
  - Blood sugar thresholds: FDG-PET brain < 175 mg/dL, FDG-PET whole body <250mg/dL
- Gastric emptying study:
  - Patient must tolerate PO (consume a standardized meal in 10 minutes), best performed as outpatient study

MUSCULOSKELETAL PROTOCOLS: if questions: page MSK IR on-call radiologist at p36321

CHEST X-RAY



Red line outlines optimally placed central line. Dotted line denotes carina.

1. **Line placement**
   - o ETT positioning: tip 3 - 7 cm above the carina in an adult
   - o SVC: b/w R tracheobronchial angle and R heart border (Chest 1998;114:820)
   - o Superior cavoatrial jxn: ~2 vertebral bodies below the carina (JVIR 2008;19:359)
   - o Line positioning:
     - ▪ PICC or Central line: tip in the lower SVC or at the superior cavoatrial jxn
     - ▪ HD catheter: tip in the right atrium
   - o Post placement: check for pneumothorax, except with PICC/midline (see below)
2. **Pneumothorax**
   - o Sensitivities:

Imaging Position	Detectable PTX Size	Imaging Findings
Supine/Portable	500 cc (LEAST Sensitive)	Deep sulcus sign, lucency along mediastinal border
Upright	50 cc	Sharp pleural edge, absence of distal lung vessels
Lateral decubitus	5 cc (MOST sensitive)	Nondependent collection of air

   - o Tension: contralateral mediastinal and tracheal shift, collapse of ipsilateral lung, flattening of ipsilateral hemidiaphragm, widening of ipsilateral rib spaces
   - o Artifacts that mimic visceral pleural lines: (BMJ 2005;330:1493)
     - ▪ Skin folds: form an interface (not a line), extension beyond rib cage, presence of distal lung vessels
     - ▪ Medial border of scapula: extension beyond rib cage w/ rest of scapula

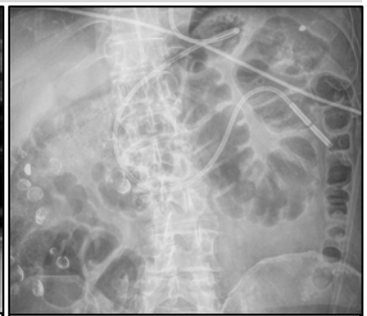
Bilateral pleural effusions

3. **Pulmonary edema (example images)**
   - o Vascular redistribution (first sign): increased caliber of pulmonary vessels in upper lobes ("cephalization")
   - o Interstitial edema: incr. interstitial opacities, indistinct pulmonary vasculature, **Kerley B lines** (peripheral subpleural linear opacities), peribronchial cuffing
   - o Alveolar edema: perihilar/central opacities, pleural effusions, cardiomegaly
   - o Pearls: typically bilateral and symmetric, rapid appearance/resolution of findings
   - o Pitfalls: low lung volumes mimic increased interstitial opacities via crowding of normal vasculature

ABDOMINAL X-RAY (KUB)

1. **Line placement**
   - For Decompression: gastric fundus or dependent portion of stomach. Side-port AND tip should be 4-6 cm below the GE junction.
   - For Feeding: distal duodenum or proximal jejunum; C-loop of duodenum is only reliable indicator of post-pyloric placement
   - Post placement Assessment: check for endobronchial placement. Should descend vertically in midline, pass diaphragm, tip should be visualized

Enteric tube (decompression) – arrow shows side port


Feeding tube - weighted tip in proximal jejunum

2. **Small bowel obstruction** (RadioGraphics 2009;29:423)
   - **KUB**: preferred initial examination
     - o Assess for: small bowel dilatation >3 cm, decompressed distal small/large bowel, air-fluid levels, stacked loops of bowel, free air as a complication
     - o Main differential: post operative ileus → often large bowel is also dilated
   - **CT**: equivocal cases / further evaluation
     - o Findings: SB dilatation with collapse of distal bowel loops and transition point
     - o Severity:
       - ▪ Partial: passage of air or contrast beyond the obstruction
       - ▪ Complete: no passage of air or contrast beyond the obstruction
     - o Transition point: look for small-bowel feces sign (fecal material mixed with gas bubbles in small bowel just proximal to transition point)
     - o Common causes: adhesions, Crohn's, malignancy, hernias; colon cancer most common cause in LBO
     - o Closed loop obstruction: radially oriented bowel loops, engorged mesentery, whirl sign
     - o Strangulated/incarcerated hernia (ischemia): bowel wall thickening, lack of bowel wall enhancement, pneumatosis intestinalis, portal venous gas

Small bowel dilation in case of small bowel obstruction (SBO)

3. **Pneumoperitoneum** (AJEM 2009;27:320)
   - Upright: air beneath the diaphragm
   - Left lateral decubitus: air overlying the liver
   - Supine: **insensitive** exam

Pneumoperitoneum

ULTRASOUND

1. **Cholecystitis** (AJR 2011;196:W367)
   - US is preferred initial examination
   - Common findings: gallstones, gallbladder wall thickening >3 mm, gallbladder distension (>4cm transverse, >8cm longitudinal), peri-cholecystic fluid
   - Sonographic Murphy's sign: 92% sensitivity (analgesics reduce sensitivity, unreliable if recent analgesics)
   - Gallstones and gallbladder wall thickening: 95% positive predictive value for acute cholecystitis
   - Key Differential - Gallbladder wall thickening without stones and without distension is more likely to be from third spacing (CHF/renal failure/cirrhosis) or underlying liver disease (hepatitis); much less likely cholecystitis
2. **Deep venous thrombosis** (Cardiovascular Diagnosis and Therapy 2016;6:493)
   - Compression U/S: noncompressibility of vein (*key finding*), echogenic thrombus within vein, venous expansion
   - Venous duplex U/S: absence of color Doppler signal, flow phasicity, & response to augmentation maneuvers
   - Non-obstructive vs. Obstructive thrombus: both are non-compressible, obstructive lacks color Doppler flow
   - CT venogram:
     - Alternative to U/S in critically ill patients who have undergone CT PE
     - Pros: evaluation of pelvic veins and IVC, which are difficult to assess on US
     - Cons: invasive, requires contrast, radiation, possible streak or mixing artifacts

CROSS SECTIONAL IMAGING

Excellent resources for anatomy, image interpretation, and sample cases: https://radiopaedia.org/; https://radiologyassistant.nl/; https://introductiontoradiology.net/; https://www.learnabdominal.com/ (GI/GU); http://xrayhead.com/ (MSK)

CT Head Example Search Pattern

1. **Brain parenchyma**
   a. Mass lesion: brain window
   b. Intraparenchymal hemorrhage: brain window
   c. Infarction: stroke window
2. **Epidural / Subdural Hematoma**
3. **Vessels**
4. **CSF spaces**: ventricles, sulci, basal cisterns
5. **Midline shift or herniation**: coronals helpful
6. **Soft tissues** (great to start with for trauma head CTs)
7. **Bones/sinuses**

MRI Brain Example Search pattern

1. **Brain parenchyma**
   a. Mass lesion: T1, T2, FLAIR
   b. Intracranial hemorrhage: SWI, T1, T2
   c. Infarction: DWI, ADC
2. **Vessels**: T2 for flow voids, T1 post-contrast, TOF if non-contrast MRA
3. **CSF spaces**: T2
4. **Midline shift or herniation**: coronals helpful
5. **Soft tissues**
6. **Bones/sinuses**

CT Chest Example Search Pattern

1. **Lines and tubes** (scout can be very helpful)
2. **Upper Abdomen**
3. **Soft tissues**
4. **Bones**
5. **Heart and mediastinum**: thyroid, lymph node stations, heart and pericardium, asc/desc aorta, great vessels, esophagus
6. **Pleura**: pleural effusion, pneumothorax
7. **Airways**: trachea, bronchi, bronchioles
8. **Lungs**: pathology manifests as changes to the secondary pulmonary lobule (see links)
   a. Radiology Assistant → Lung HRCT Basics
   b. Radiopedia → Lobule Basics

CT Abdomen/Pelvis Example Search Pattern

1. **Lung bases and partially visualized heart**
2. **Liver/gallbladder**: focal lesions, biliary dilatation
3. **Spleen**
4. **Pancreas**: focal lesions, pancreatic ductal dilatation
5. **Adrenals**
6. **Kidneys/ureters**: hydronephrosis, stones, focal lesion
7. **Bladder/Prostate/Uterus/Adnexae**
8. **Peritoneum**: free air or fluid
9. **Lymph Node Stations**
10. **Vessels:** AAA
11. **GI tract**: bowel distension, bowel wall thickening, appendix, terminal ileum
12. **Soft tissues**
13. **Bones**

Procedures Ultrasound Basics

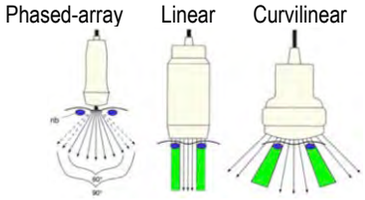
REMINDER: do not base clinical decisions on POCUS exams unless the exam and decisions are supported by a supervising provider. Additionally, POCUS should be used in the setting of *limited and targeted clinical questions.*

EQUIPMENT (NEJM 2011;364:749)

Basic Terminology:

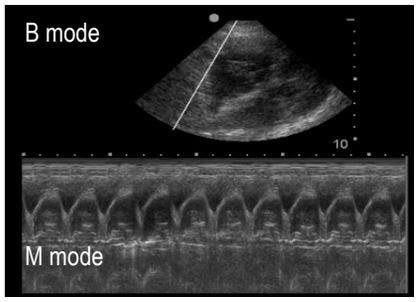
- Frequency: 1Hz = 1 cycle/sec; medical US typically between 2-15MHz
  - High frequency (>5MHz): ↑resolution, shallow tissue penetration, ideal for **vascular, skin, breast, thyroid**
  - Low frequency (2–5MHz): ↓resolution, deeper tissue penetration, ideal for **abdominal, OB/GYN, cardiac**
- Gain: signal amplification; similar to brightness control. Higher gain = brighter image; lower gain = dimmer image
- Depth: depth of field of view (FOV). Excessively large FOV = ↓spatial resolution; tight FOV limits view of nearby structures
- Attenuation: reduced signal transduction through a medium = ↓signal intensity behind it (bone/air/stones have high attenuation)

Transducer (**probe**): converts electricity into sound waves → transmits sound wave into tissue → receives sound waves echoed back from tissue. Indicator (denoted by dot or notch on probe) displays on **left of the screen**. *Exception*: echocardiography → indicator displays on **right side**. For most indications, position probe with indicator to patient's right or cranially



- PHASED-ARRAY (cardiac) probe: good for looking in small windows (i.e. between intercostal spaces for cardiac or pulm imaging); low resolution, fan-like image
- LINEAR (vascular) probe: good for shallow structures (i.e. vascular, soft tissue). Uses high frequency with good resolution, produces rectangular image
- CURVILINEAR (abdominal) probe: good for deeper structures (i.e. intra-abdominal). Uses lower frequency; combines linear and phased-array probe image qualities

COMMONLY USED MODES



- B-mode (brightness mode): standard 2D gray-scale image
- D-mode (doppler mode): detects flow to or away from transducer. Useful to find and define vessels, or flow across valve
  - Color → direction and velocity are color coded and superimposed on B-mode image. "**BART**" (Blue is Away from probe, Red is Towards)
  - Power → detects very low flow but not direction, useful in vascular compromise
  - Spectral → velocity presented graphically on a timeline
- M-mode (motion mode): takes a slice of a B-mode image over time. Often used in TTE. Useful to assess lung sliding for pneumothorax

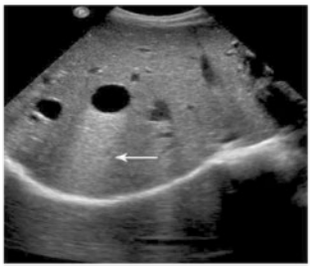
GENERAL IMAGING CONCEPTS

Typical Appearance of Normal Tissue:

Acoustic Shadowing (gallstone)

- Skin and pleura are smooth and brighter than surrounding tissue (**hyperechoic**)
- Fat and muscle are darker (**hypoechoic**), though varies depending on the tissue
- Fluid (e.g. blood, effusion, ascites) is black on US (**anechoic**), though thick fluids (e.g. pus) can be brighter than typical fluid. Fluid can have a layered appearance based on density.
- Tendons and nerves are bright (**hyperechoic**) if perpendicular to probe, dark (hypoechoic) when angle is changed (anisotropy)
- Bone has a hyperechoic rim (due to reflection) with dark shadow beyond it

Artifacts: elements seen on ultrasound image that do not exist in reality


Acoustic Enhancement (liver cyst)

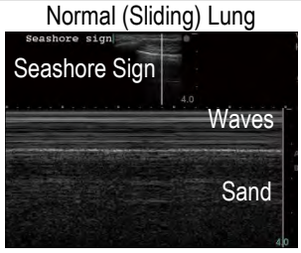
- Reflection: proportional to the difference in acoustic impedance between two tissues (↑difference = ↑reflection)
- Relative acoustic impedance: bone > solid organ > fat > lung > air
- Shadowing: signal beyond strongly attenuating/reflecting structure (e.g. stones, bone)
- Enhancement: signal posterior to weakly attenuating (hypo or anechoic) structure (e.g., cysts)
- Mirror image: structures in front of strong reflector (e.g. diaphragm) appear to lie behind it as well
- Reverberation: evenly spaced lines at various depths beyond a strong reflector (e.g. A lines beyond pleura)
- Comet tail: tiny, narrow reverberations beyond very strong reflector (e.g. metal pellet) blending into a line

IMAGING AND TIPS (see The POCUS Atlas for reference)

Diagnostic Use:

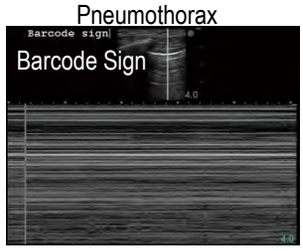
- **Pneumothorax**: use LINEAR (vascular) or CURVILINEAR probe. In supine patient, look in 3rd intercostal space on anterior chest, pointing indicator cranially. Identify hyperechoic rims of the ribs with posterior shadowing. The pleura is the hyperechoic stripe that is within the intercostal space. Normal lung will slide along the pleural line with respiration, while pneumothorax will not. If ambiguous, use M mode to confirm. A lack of lung sliding will change the normal 'seashore' sign to a static 'barcode' sign. Sn 91%, Sp 98%, superior to CXR. Can also look for "lung point" (100% specific) (J Emerg Trauma Shock 2012;5:76; Annals EM 2013;61:207)

Normal (Sliding) Lung



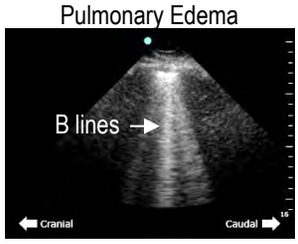
- **Pulmonary embolism**: use PHASED-ARRAY (cardiac) probe. Bedside US can be used to identify right heart strain. Look for RV size ≥ LV size, septal bowing (D-sign in parasternal short), note Sn 53%, Sp 83% for PE. RV/LV ratio most easily visualized in apical 4 chamber view, can be misleading based upon slight changes in plane. Assess the cardiac septum vertical and in line with midpoint of probe. Combine with parasternal axes for better reliability (J Am Soc Echocardiogr 2017;30:714)

Pneumothorax



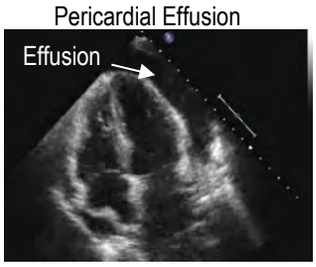
- **Pulmonary edema**: use PHASED-ARRAY (cardiac) or CURVED (abdominal) probe. Evaluate the lung between rib spaces and across multiple lung fields similar to auscultation. Look for B-lines: comet like artifacts that shine perpendicular from the pleural line and obliterate A-lines. ≥3 in one interspace is consistent with interstitial fluid, and bilaterally suggests pulmonary edema. Ddx of B-lines is broad. Operator dependent but can outperform CXR (Intensive Care Med 2012;38:577; Acad Emerg Med;23:223)

Pulmonary Edema



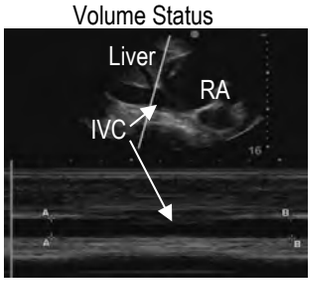
- **Pericardial effusion**: use PHASED-ARRAY (cardiac) probe. Look for an anechoic collection between the heart and the hyperechoic pericardium. Hemorrhagic or purulent effusions may appear more complex. On parasternal long axis, pericardial effusion will be anterior to the descending aorta while a pleural effusion will be posterior. All four views are important but subxiphoid often used in emergencies. Look for chamber collapse indicating tamponade: RA is more sensitive; RV is more specific (Resuscitation 2011;82:671)

Pericardial Effusion



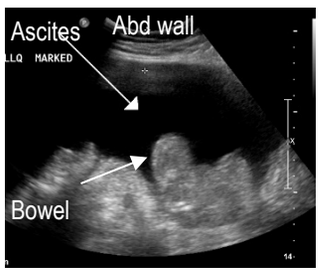
- **Volume status**: use the PHASED-ARRAY (cardiac) probe. IVC collapsibility has been proposed as a proxy for CVP and fluid responsiveness, though data is mixed. There are no consensus guidelines. Start with subcostal view of RA/RV, then rotate probe to the sagittal plane to find the IVC draining into RA and abutting the liver. Look at IVC 2cm from RA: fluid responsiveness or an underfilled IVC is suggested by 1) IVC diameter ≤1.5cm and 2) IVC collapses ≥½ its diameter with inspiration. Can use M mode to assess collapsibility. IVC diameter ≥2.1cm with ≤50% inspiratory collapse can indicate elevated CVP. Pair IVC POCUS w/ lung US for volume status evaluation. (Crit Care 2012;16:R188; CCM 2013;41:833; Shock 2017;47:550)

Volume Status



Procedural Use: *refer to pages on specific procedures for more details*

- **Paracentesis**: use CURVILINEAR (abdominal) probe. Locate largest fluid collection, often in LLQ. Try rolling patient to side to increase pocket size. LINEAR (vascular) probe can help identify any overlying vessels (particularly inferior epigastric vessels). Bowel appears as hyperechoic finger-like projections within the anechoic ascites, ensure prior to procedure scanning in multiple locations and fanning to assess for bowel (to avoid perforation). Measure the depth of the abdominal wall and compare to your needle to determine when to expect flash.



- **Central venous access**: use LINEAR (vascular) probe. Reduces complications and quality of placement compared to landmark approach (Crit Care 2017;21:225)
  - In-plane (longitudinal): can view entire tip, but harder to keep needle in view
  - Out-of-plane (cross sectional): easier to center needle, may underestimate depth

- **Peripheral IV**: use LINEAR (vascular) probe. Most of your time should be spent finding the best vein to go for. Evaluate anterior forearm prior to assessing the cephalic in upper arm. Track along vessel length to determine trajectory, look for large, superficial, compressible vessels that are not immediately adjacent to pulsatile, non-compressible arterial vessels

Procedures Ultrasound-Guided Peripheral IV

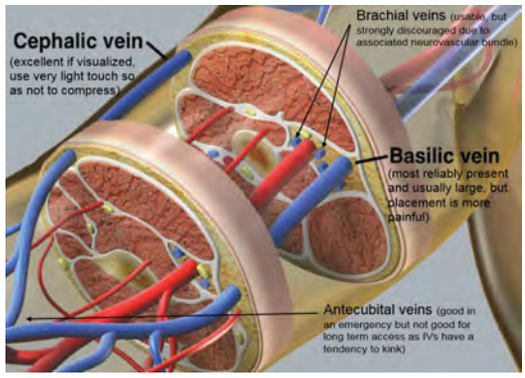
General Considerations

Indications: non-emergent access in a patient with difficult access. *If emergent, obtain IO or central access*
Locations: forearm first; then AC, cephalic, basilic, brachial; larger veins offer higher chance of success than smaller veins (see figure)
Contraindications: relative: sensory/motor deficits (clot risk), HD fistula, hx of LN dissection, overlying infection/cellulitis
Materials: angiocath (18 or 20G best; small IVs not well visualized on US), vascular probe, gel/sterile lubricant, tourniquet, alcohol wipe/chlorhexidine, tegaderm, extension tubing, saline flush, ± vacutainer adapter and tubes/cultures + labels (if labs needed)

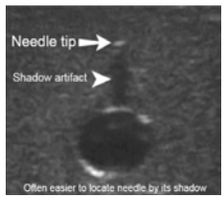
- Angiocath selection: standard length (30mm) good for vein <0.8cm deep; long needle (48mm) preferred for ≥0.8cm deep (48mm 18G [green] stocked in most supply rooms, but 48mm 20G [pink] more difficult to find.

Transverse Technique

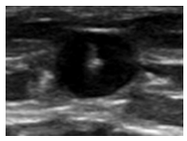
NEJM 2012;366:e38: *choosing a vein (8:45), transverse (10:05), longitudinal (12:28)*


Cephalic vein
(excellent if visualized, use very light touch so as not to compress)
Brachial veins (usable, but strongly discouraged due to associated neurovascular bundle)
Basilic vein
(most reliably present and usually large, but placement is more painful)
Antecubital veins (good in an emergency but not good for long term access as IVs have a tendency to kink)

1) **Setup**: positioning is crucial. Place US on opposite side of pts bed, adjust bed to appropriate height, obtain seat if needed, abduct & externally rotate pts arm
2) **Place tourniquet**: place tourniquet proximal, near axilla if possible
3) **Confirm anatomy**: use vascular probe at minimum depth to locate adequate superficial veins, M-mode line can be helpful to stay centered
   - Find vessels: start at AC and move proximal first, then distal. Key is to find LARGE vessels (>0.4cm diameter) that are CLOSE to the surface (depth between 0.3cm – 1.2cm) (J Emerg Med 2010;39:70). Common veins: basilic, cephalic > deep brachial (see figure)
   - Confirm venous: gentle pressure differentiates non-thrombosed veins (fully compressible, non-pulsatile) and arteries (poorly compressible, pulsatile); color doppler can confirm; scan both arms if able
   - Trace vessel course: follow the vessel course proximally and distally; recognize and avoid branch points, diving veins, and irregularly coursing veins → identify the trajectory along which the ultrasound probe travels to maintain center of vessel
4) **Sterility**: use alcohol pad or chlorhexidine swabs to sterilize proposed venipuncture site; clean US probe, then cover with tegaderm; use sterile lubrication (or sterile US gel) as conduction medium for probe (can also put gel under tegaderm)
5) **Orient ultrasound**: center target vein on US screen, confirm with compression, confirm vein course is in line with proposed needle course, stabilize probe by anchoring 5th finger/hand on patient
6) **Insert angiocath**: with *bevel up*, puncture skin and advance angiocath 2-3 mm at a 45° angle
   - Angiocath needle tip should be *centered on US probe* – this will be directly over the vein if vein is centered on screen
   - Insertion site at skin is *distal* to the planned site of insertion into vein
   - At skin insertion, eyes should be on the *site of venipuncture*, not on the US screen, though after puncture, should be watching screen at all times and not hand

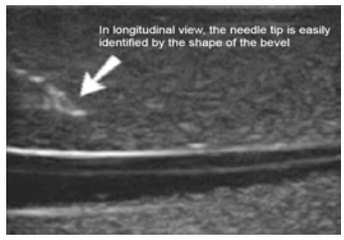


7) **Find tip and advance**: needle tip (and shadow) should appear on screen → advance PROBE until you lose needle tip → advance NEEDLE tip until it reappears on US screen; continue to advance until tip is "tenting" the roof of the vein
8) **Enter vein**: a quick short jab will allow you to enter vein; visualize needle tip as "target sign" (see image)
9) **Drop angle and advance**: drop your hand to flatten needle angle; continue to advance as above, keep needle in center of vein (always aim to get "target sign" with each probe then needle advancement) until angiocath is hubbed to skin, then retract needle



10) ***Alternative:* Slide off catheter**: once 3-5mm into vein, can slide catheter off needle into vein and hub, and retract needle
11) **Flush**: attach extension tubing, pull back on saline flush (ensure drawback), REMOVE TOURNIQUET, flush with saline → can also confirm lack of extravasation of saline under US visualization
12) **Secure**: secure catheter and tubing with Tegaderm, +/- additional tape; nurses may redress IV

Longitudinal Technique: use the following adjustments to the above technique



1) Identify target vein in the transverse view
2) **Rotate the probe to obtain a longitudinal view with the indicator towards your needle**
3) Align needle in the plane of the probe; puncture skin at 45 degrees, visualize needle tip
4) Advance needle until you can see that the tip of the catheter itself is fully within the vein
5) Do not to go through the back wall. Advance the catheter under direct visualization

Technique	Pros	Cons
Transverse (short axis)	- Faster, requires less finesse with US probe - Allows visualization of adjacent structures	- Harder to visualize the needle tip - Risk of "through and through"
Longitudinal (long axis)	- Improved visualization of the needle tip (depth) - Can advance catheter under direct visualization	- Challenging to maintain probe/vein/needle in plane - Cannot see adjacent structures

Troubleshooting (Transverse Video; Longitudinal Video; written guide: West J Emerg Med 2017;18:1047)

- *Can't see needle:* **gently** bounce the needle tip to generate artifact or slight fanning of the ultrasound probe until the tip is in view
- *Too much loose tissue:* use tape or have someone assist by putting tension on the tissue w/o applying pressure over target vein
- *Vein rolls:* reposition directly over the middle of vein, use a slightly steeper angle to take advantage of the sharp edge of the needle
- *Trouble finding any veins:* try using a blood pressure cuff high in the axilla instead of a tourniquet, but give the patient frequent breaks

Procedures

Central Line

General Considerations

Indications: hemodynamic monitoring (CVP, CVO_2); admin. of noxious meds (pressors, chemo, hypertonic solution, TPN); rapid large volume resuscitation (Cordis/MAC); inadequate peripheral access; HD/CVVH/pheresis; to introduce other devices (PA line, temp wire)
Contraindications: vein thrombosis or stenosis should prompt another site. Coagulopathy/thrombocytopenia are relative contraindications. If severe coagulopathy, avoid subclavian (not a compressible site & difficult to effectively monitor for bleed)
Site selection: general preference at MGH is RIJ > LIJ > subclavian/femoral due to historical concern for infection. However, more recent data suggests no difference between these sites with proper attention to sterile technique (NEJM 2015;373:1220). Additionally, it is helpful to predict if RIJ may be needed for dialysis catheter, in which case LIJ placement is preferred.
Catheter selection: select based on number of lumens and speed of infusion; if rapid infusion required → large bore, short length (Cordis/MAC). *Right IJ* catheter length: 16cm. *Left IJ* catheter length: 20cm
Alternatives: PICC (if no concern for bacteremia, often requires negative BCx >48hr) or IO (if emergent, should not be used for >24h)
Infection control: scheduled exchange of catheters without evidence of infection is **NOT** indicated. Cultures drawn from indwelling catheters have **↑false ⊕ rate**; generally not done aside from time of sterile placement (NEJM 2003;348:1123)

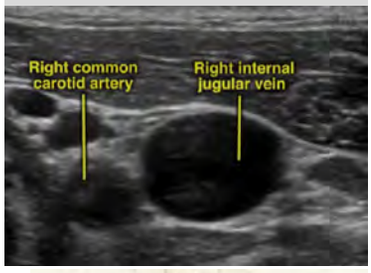
Internal Jugular Vein (Video: NEJM 2010;362:e57)

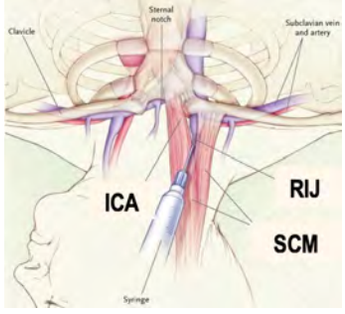
Advantages	Disadvantages
Compressible vein	Carotid artery puncture 2-10%
Lower risk of pneumothorax (< 1%) than subclavian	Less patient comfort
Ability to use real-time ultrasound	Anatomy not as consistent as subclavian

All IJ CVCs placed with real-time US guidance at MGH: ↓first attempt failure, procedure time, and failure/complication rate
Positioning: supine + Trendelenburg to engorge veins & ↓risk of air embolus. Towel can be used to elevate shoulder to lateralize IJ. Site selection (typically R > L, unless preserving right side for HD line).

- Locate triangle formed by medial and lateral portions of SCM with the clavicle as base
- Find IJ, typically superficial and lateral to carotid, compressible; can also use color Doppler
- RIJ generally preferred due to direct course to SVC, LIJ ↑risk of PTX and thoracic duct injury

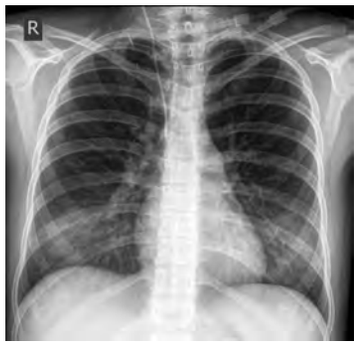
Transverse ultrasound view showing RIJ anterior & lateral to carotid artery





Target: aim at ipsilateral nipple, 45 degrees (map out trajectory of vessel using ultrasound)

1) Preparation and positioning are ESSENTIAL; ensure someone is always available to help
2) Obtain consent; perform TIME-OUT with RN; complete checklist with RN assistance
3) Use US to ensure your target anatomy is in good position. Assess LIJ & RIJ
4) Use 2% chlorhexidine solution to prep (in the kit); drape the entire patient in sterile field
5) Place caps on CVC, flush all lines with sterile saline, remove cap from brown port **(where wire will emerge)**; ensure guide wire advances easily and syringe comes off needle easily
6) Locate IJ vein & carotid artery using ultrasound
7) Anesthetize with lidocaine; can make wheal & inject along tract (aspirate before injecting!)
8) Insert (bevel up) large bore needle at the apex of SCM/clavicle triangle, about 4-5 cm above suprasternal notch. Advance @ 45° towards ipsilateral nipple visualizing tip with US; apply negative pressure throughout. Once flash of blood is obtained → stop advancing the needle, continue to draw back venous flow (dark, non-pulsatile)
   - If arterial flow seen, remove needle and compress ~10 min
   - If air drawn back, suspect PTX → STAT CXR, 100% FiO_2, decompress if tension
9) Once flow obtained, drop US probe and stabilize needle with your non-dominant hand, flatten needle angle while drawing back to ensure continued flow, remove syringe from locator (occlude hub with thumb to minimize risk of air embolism in non-ventilated patients)
10) Feed the curved end of the loaded wire into the needle (*never* feed the opposite end), **NEVER LET GO OF THE WIRE**.
    - If any resistance, remove wire, assess for flow w/ syringe; if good blood flow, try twisting wire or flattening angle of needle
    - For RIJ → feed ~25cm of wire (between two and three dark lines) → watch for ectopy (suggests wire in RV → withdraw)
11) Remove needle over guidewire
12) Confirm wire is in vein using US in transverse and longitudinal planes
13) Perform manometry confirmation → advance angiocath from kit over wire, remove wire, connect manometer tubing → leave fluid in manometer and hold vertically to avoid air embolism → venous blood should be non-pulsatile, dark, and rise <20cm → disconnect manometer tubing → replace wire through angiocath → remove angiocath
14) Extend puncture site with scalpel (face cutting edge away from wire to prevent cutting wire)
15) Thread dilator over wire (using twisting motion, grip near the skin) until about 1/3 is inserted, then remove; goal is to dilate skin/subcutaneous tissue, NOT the vessel itself (increased bleeding); ensure the wire moves back and forth freely while dilating (may otherwise be kinked)
16) Advance catheter over wire (wire comes out brown port); remove wire
17) Draw back vertically off all ports through caps using saline flush (only small amount of flash needed), flush all lines clean, clamp ports
18) Secure with sutures; place Biopatch prior to securing with dressing
19) Order CXR (ASAP) to assess position, rule out PTX/hemothorax; MUST **look at the CXR yourself to confirm placement**; catheters should terminate in superior vena cava or cavo-atrial junction; may need to pull back if in RA (→ ectopy). If adequate position, put in order "OK to use"
20) Write procedure note (create note in notewriter, then select "Central Line")



Procedures Central Line

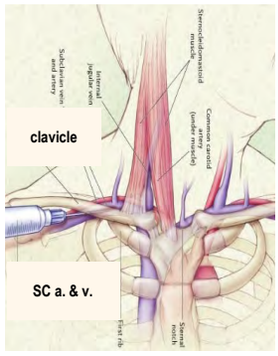
For subclavian or femoral vein access, please discuss with attending and ensure appropriate oversight prior to procedure!

SUBCLAVIAN VEIN (Video: NEJM 2007;357:e26)

Advantages	Disadvantages
Anatomy more reproducible, incl obesity, w/ bony landmarks	Risk of PTX (**1-8%**), L side slightly > R, higher dome of L pleura
Improved patient comfort; easier to dress and maintain	**Not easily compressible**; more risk a/w bleed if coagulopathic
	Risk of subclavian artery puncture/hemothorax (0.5-1%)

Positioning: place in Trendelenburg to engorge vein and consider placing a roll of towels between the scapula to expose subclavicular area (may distort anatomy for some)
Entry: at MGH → infraclavicular approach (as opposed to supraclavicular); puncture skin 1cm caudal to junction of medial 1/3 and middle 1/3 of clavicle (where vein flows just under the bone)
Target: bevel up and aim toward sternal notch, 30° to the skin; needle should advance just on the underside of the clavicle (~3-5cm depending on anatomy); some people "walk down" the clavicle to ensure this, but may lead to dulling or bending of needle as well as periosteal pain
Pearls:

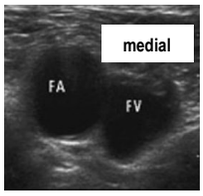
- Turning head to ipsilateral side will kink IJ and facilitate wire going down the SVC
- Rotate bevel 90° caudal after needle is in the vein to help direct wire into the SVC
- Ultrasound not always helpful (given acoustic shadowing from bone)
- Subclavian vessels may be compressed with two fingers squeezing around the clavicle
- Guidewire usually only needs to advance 20cm (two dark lines)



FEMORAL VEIN (Video: NEJM 2008;358:e30)

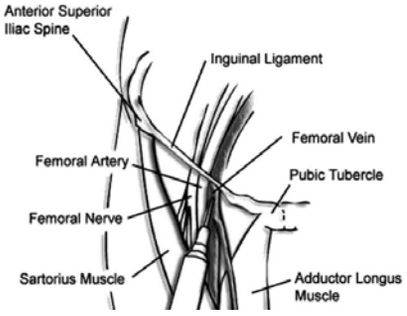
Advantages	Disadvantages
Compressible	Femoral artery puncture 5-10%
No risk of PTX	Risk of development of DVT
Can be cannulated more easily during CPR	Less patient comfort in hip flexion, requires immobility
Large caliber vein technically easier to cannulate	May occlude flow if patient has obesity
	Caution in patients with inferior vena cava filters

Positioning: head of bed flat; abduct lower extremity and externally rotate the hip, generally use 20 cm line
Entry: bevel up, 2-3 cm below inguinal ligament, 1cm medial to palpated pulse → femoral vein lies medial & inferior to the femoral artery



- If non-urgent, best to use US to visualize
- "**NAVEL toward the NAVEL**" → Nerve, Artery, Vein, Empty, Lymphatics (alternative: venous → penis)
- Two fingerbreadths lateral to pubic tubercle if pulse not palpable
- DO NOT approach vein above inguinal ligament → increased risk for RP bleed & peritoneal perforation

Target: directly superior at 30-45°
*No confirmatory imaging needed



HEMODIALYSIS LINES

Sites: IJ (R preferred), subclavian vein, femoral vein
Placement technique: Same steps as CVC placement, additional dilation step is key difference (double dilation). For manometry, can use catheter from Arrow arterial kit. Note, the wire will come out of the blue colored port.

CORDIS (AKA VENOUS INTRODUCER SHEATH)

Combined dilator and sheath w/ side port for IV access
Indications: rapid resuscitation, introducer sheath for PA catheter, temp wire placement
Sites: IJ (R preferred for PA line), subclavian vein, femoral vein
Placement technique: uses Seldinger technique (advance catheter over a wire) but dilator and sheath are advanced over wire together as unit; dilator and wire then removed together; side port aspirated and irrigated prior to use

CVC COMPLICATIONS

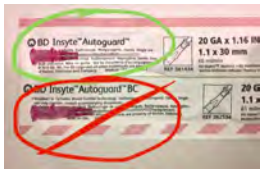
Arterial puncture: hold pressure x10min; compress 1 inch inferior (IJ) or 2 inches superior (femoral) to puncture mark
**Methods for ensuring venous placement include manometry/waveform measurement, ABG sampling*
Dilation/line placement in an artery: consult vascular surgery BEFORE removing line; consider CT if pt stable
Pneumothorax (IJ & subclavian): suspect if hypoxemia, hypoTN, difficult stick; obtain STAT CXR → consult thoracic surgery if PTX or hemoTX; if tension physiology (shock) → immediate decompression with 16G angiocath at 5th ICS, mid-axillary line (enter above the rib)
Retroperitoneal bleed (femoral): suspect if hematoma or hypotension; STAT CT → consult vascular medicine
Loss of wire or wire stuck in vessel: remove needle, DO NOT use excessive force to pull out wire if it is stuck → leave in place, hold pressure to prevent exsanguination → STAT KUB/CXR if wire loss → consult vascular medicine

Procedures

Arterial Line

General Considerations

Indications: real-time BP monitoring (pressors, HTN emergency, CVA); frequent ABGs, softer indication for lab draws (≥3 per day)
Locations: radial > femoral > dorsalis pedis > axillary; brachial not recommended given lack of collaterals unless placed by anesthesia
Contraindications: lack of sufficient collaterals (abnormal Allen test), h/o arterial grafts/stents, Raynaud's/scleroderma
Risks: pain, infection, bleeding, ischemia, vasospasm, arterial dissection, embolization, necrosis, loss of limb
Materials: arm board, tape, Chux, chlorhex prep, 4 x 4 sterile gauze, pack of sterile towels, sterile gloves, mask, eye protection, bouffant, 20G angiocaths, guide wire, Tegaderm, US probe cover (if needed). Pre-assembled kits available.



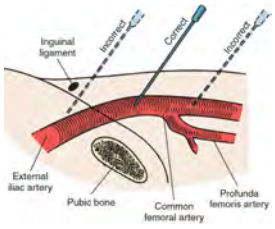
- If pt awake → consider lidocaine w/o epi (small syringe and 25G needle)
- **Use PINK SOLID STRIPE angiocath**; do NOT use pink interrupted stripes, which has a one-way valve so can't pass wire
- Alt: use Arrow arterial line / Micropuncture kit; the kit's longer catheter is preferable for femoral site

Radial Technique (Video: NEJM 2006;354:e13)

1) Obtain consent and perform TIME OUT; ask RN to prepare for A-line
2) Confirm anatomy by palpating pulses or with US. Test for collateral circulation of the hand:
   - **Allen test**: make fist for ~30sec, then occlude ulnar & radial arteries; pt opens hand (palm should be blanched); then release pressure from ulnar artery → palm should regain color within ~5-10 sec
   - **Modified Allen test**: place pulse oximeter on index finger or thumb; occlude radial and ulnar arteries until wave form lost; release ulnar artery → should get arterial tracing if good collateral flow
3) Proper positioning: adjust bed to appropriate height for operator comfort. Put Chux under wrist; extend pt's wrist; secure arm board (bendable arm boards in CCU and MICU). Consider taping hand to bed/table to stabilize; note the course the artery travels.
4) Sterilize wrist widely with 2% chlorhexidine swabs for ~30 seconds; open towel packet to create sterile field
5) Prepare field: drop angiocath & guide wire (and sterile US supplies) on sterile field; don sterile gloves and drape widely w/ sterile towels. Prepare US with gel and probe cover, if utilizing. Leave on sterile field
6) Prepare angiocath/guidewire: check angiocath to ensure catheter slides easily off needle; pull one side of wire *slightly* out of paper
7) Pick your target: palpate radial artery (or visualize with US) with non-dominant hand; plan to puncture distal to the pulse you palpate. *Note: Avoid catheterizing very distal (near angle of extension) as A-line more likely to displace later when pt moved*
8) Insert angiocath: with *bevel up*, advance angiocath needle at a 45° angle toward pulse until flash is obtained (similar to ABG)
9) Once flash obtained, go *"through-and-through"*: advance ~0.5cm through artery; hold the top of the plastic catheter with non-dominant hand; push button to retract needle, while steadying the catheter (should be no blood flow)
10) Hold guide wire close to head of angiocath w/ dominant hand
11) Level and pull back : lower angiocath as parallel to skin as possible and SLOWLY pull it back until pulsatile blood flow is obtained, then hold angiocath very still to avoid pulling out of vessel
12) Advance wire: insert the wire into the angiocath; should not feel resistance; if unable to advance wire, DO NOT LET GO OF GUIDE WIRE; TRY SPINNING THE WIRE → avoids side branches of artery (where wire commonly gets caught)
13) Advance angiocath into the artery over the wire (Seldinger technique)
14) Remove guidewire: apply pressure to radial artery proximal to cath; remove guide wire; occlude opening of the angiocath with finger
15) Connect transducer: ask RN for A-line setup and connect transducer to angiocath; RN will flush; confirm placement w/ art. waveform
16) Clean the area with gauze and dress with a Tegaderm; MICU RNs will often re-dress afterwards, so ask their preference; in ED, suture to the wrist; NWH has snap dressings

Alternatives and Troubleshooting

- **If using Doppler**, mark out course of artery with marking pen
- **If using US,** can try advancing needle under US guidance and once firmly in vessel, advance catheter over needle (no guide wire; similar to PIV)
- After multiple attempts, the artery may spasm or hematomas may form. Pursue alternative site (or more distal site).
- If unable to thread guide wire after attempting spinning during insertion, consider micropuncture wire (with supervision). May help with atherosclerotic arteries at ↑risk of perforation. Kit includes introducer needle, microwire, and microcatheter w/inner stylet.
  - Use micropuncture needle to puncture vessel under US guidance until flash, can walk forward in vessel, then drop probe
  - Thread microwire (more pliable end first) through needle, then remove needle
  - Thread microcatheter over the wire
  - Once hubbed, unscrew to remove inner stylet and microwire
- Femoral artery access can be considered in difficult cases. Use the long catheter in the Arrow arterial line kit. Puncture must occur distal to the inguinal ligament to prevent RP bleed. Too distal, however, and the femoral artery will bifurcate into superficial and deep femoral vessels. The femoral artery usually transverses the inguinal ligament ~1/3 distance from pubic symphysis to the ASIS. Optimal point of skin puncture is 1-2 cm below the inguinal ligament at point where pulse is palpated, or aiming to insert immediately proximal to femoral bifurcation (*see graphic*)



Procedures

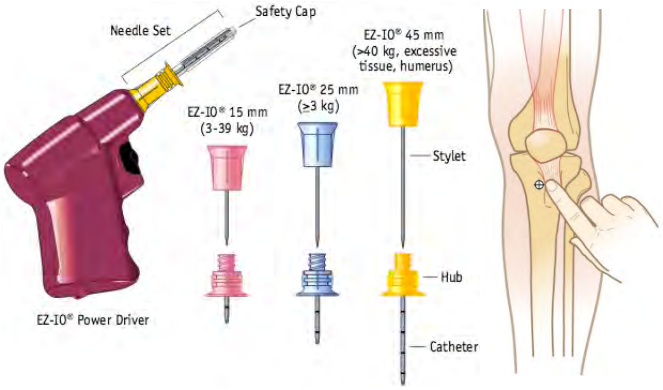
Intraosseous Line

General Considerations (Video: NEJM 2014;370:e35)

- **Anatomy**: veins that drain medullary sinuses of bones; veins supported by bones do not collapse in patients in shock
- **Indication**: patients without available IV access with urgent need (arrest, shock, status epilepticus, trauma, etc). Used for delivery of fluids/medications; labs (but tenuous – clots off quickly). Faster access than CVC, low complication risk (Resuscitation 2012;83:40)
- **Contraindications**: fractured or penetrated bone (fluids exit site), local vascular compromise (e.g. trauma or cutdown). Should be avoided in areas of cellulitis, burns, osteomyelitis, bone disease (e.g. osteogenesis imperfecta), R→L intracardiac shunts (TOF, pulm atresia) due to risk of fat emboli, failed IO insertion within 24h at same site
- **Complications**: extravasation, compartment syndrome, fracture, growth plate injury, infection, fat emboli, osteomyelitis (rare)
- **Notes**: infusion rate roughly 160mL/min at tibia or humerus with use of pressure bag, half the rate without. IO samples only accurate for some studies (Hgb, T&S, drugs, Cx). NOT for PaO2, WBC, K, AST/ALT, iCal, after drug admin

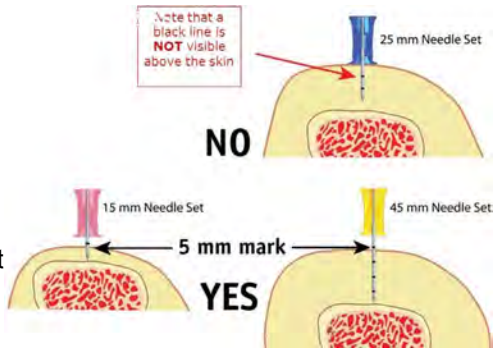
Set-Up

- **Materials**: ALL IN KIT → EZ-IO Power Driver, IO needle-set, connector tubing, 10cc syringe with saline flush, chlorhexidine/povidone iodine, sterile gloves. If awake, 3cc syringe with 1% lidocaine via 25G needle
- **Replace**: Blake 7 MICU, Materials Management (Lunder LL019)
- **Location**:
  - Proximal tibia (preferred): find the flat surface 2cm below tibial tuberosity, 1-2cm medial along tibia
  - Proximal humerus: position pt palm on abdomen (elbow flexed, shoulder internally rotated), greater tubercle 2cm below acromion process
  - Other sites: distal tibia, distal femur, iliac crest



Procedure (Crit Care 2016; 20:102)

1. Don surgical mask, eye protection, sterile gloves
2. Flush connector tubing with NS or lidocaine if patient is awake
3. Identify injection site
4. Clean injection site with antiseptic (chlorhexidine or iodine)
5. If patient is awake, create wheal with 1% lidocaine
6. Choose proper needle size: generally blue (25mm); yellow (45mm) is for excess tissue or for humerus approach
7. Magnetic pole holds the needle in place; turn the safety cap clockwise for removal
8. Hold drill perpendicular to bone if proximal tibia; hold 45° to the anterior plane and posterior medial if proximal humerus
9. Manually press the needle through the skin until it touches the bone. Confirm you see one black line on the needle (5mm mark); if not, use a longer needle (see illustration)
10. Apply gentle, steady, downward pressure while holding the trigger; allow drill to do the work
11. Release trigger when decreased resistance felt ("give" or "pop") as you enter into medullary space
12. While holding catheter in place, pull straight up to remove driver
13. Unscrew the needle stylet by rotating counterclockwise (both stylet and needle are encased in colored plastic)
14. Aspirate marrow to confirm placement. Prior to attaching tubing, send labs; blood samples may only be obtained in patients with spontaneous cardiac activity or during initial CPR before drug and fluid infusion through the IO
15. Attach connector tubing and flush IO w/ NS or 1% lidocaine over 45s if the patient is awake (IO infusions are VERY painful); if the patient is unconscious, rapid 10mL NS. Look for superficial swelling and note that no flush means no flow!
16. Apply IO dressing stabilizer – FYI each size needle has a different dressing, will not fit if using dressing for different size needle
17. Administer rapid NS bolus/blood/pressor with a pressure bag or syringe
18. Always return the IO kit to unit for resource nurse to refill



Removal

Remove **within 24 hours** of insertion once other access is obtained (not good for long term access), or if signs of erythema, swelling or extravasation. To remove: don procedure mask, goggles, non-sterile gloves. Remove IV extension tubing from needle hub. Then, place sterile syringe on needle hub (acts as handle for removal). Grasp at needle hub and rotate clockwise while pulling gently at 90-degree angle from the bone. Do not rock the syringe. Once the needle hub is out, place needle hub in sharps container. Apply pressure over IO site until bleeding has stopped and dress with gauze and tegaderm.

Max Quinn

Procedures Paracentesis

INDICATIONS (Video: NEJM 2006;355:e21)

- **Diagnostic**: new-onset ascites, unknown etiology of ascites, rule out SBP. Low threshold for patients with cirrhosis, consider concurrent RUQUS with Doppler to rule out venous thrombosis. Para w/in 24hr = better outcomes (Liver Transpl 2023;29;919).
- **Therapeutic**: Performed for abdominal pain/discomfort, diuretic-refractory ascites, respiratory compromise, abdominal compartment syndrome, adjunctive treatment of esophageal variceal bleeding (can lower portal pressures). Larve volume para ≥ 5L removed.

CONTRAINDICATIONS

- Overlying cellulitis, inability to demonstrate ascites on US, bowel obstruction/distention, acute abdomen, 2nd or 3rd trimester pregnancy
- ↑INR, ↓plt are **NOT** contraindications in cirrhosis (INR in patients with cirrhosis is NOT reflective of the risk of bleeding). There is no need to correct coagulopathy w/ FFP or platelets unless severe DIC (Hepatology 2021;74:1014).

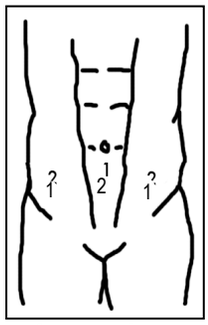
MATERIALS

- Sterile gloves, bouffant, face shield, chlorhexidine, sterile towels, US, 1% lidocaine (10cc syringe, SQ 25G needle, 1.5inch 20-22G needle), two 18G needles, 60cc syringe, diagnostic assay tubes as below, gauze, bandage or Tegaderm dressing
- Diagnostic: **20G two-way (pink) angiocath** or 18–22G 1.5inch needle. In obese pts, may use angiocath from femoral art line kit. Purple and green top tube, black top tube (for micro)
- Therapeutic: **safe-T-Centesis kit** (preferred, pigtail minimizes perforation risk) or paracentesis kit (straight rigid needle), 1L vacuum bottles, 25% albumin dosed 6-8g per liter of fluid removed if >5L (Hepatology 2021;74:1014)

SITE SELECTION/POSITIONING

- Position patient supine, turned slightly toward the side of the paracentesis, and angled upright at 30°
- Use abdominal probe to **identify fluid pocket ≥2-3cm in all dimensions** by rotating/fanning probe to ensure **absence of bowel loops**. Simulate planned angle of needle insertion with probe. Measure subcutaneous tissue and fluid pocket.
- Avoid superficial veins or prior surgical incisions and **use vascular probe with Doppler to avoid SQ vessels**
- **Approaches**:
  - LLQ > RLQ (1): **most commonly used**; LLQ ↓risk of bowel perf, use caution if pt with splenomegaly; **avoid inferior epigastric vessels** that run along lateral borders of rectus muscles

Infraumbilical (2): midline, 2cm below umbilicus; **must be certain to differentiate urine in bladder from intra-abdominal free fluid** (in practice, rarely used)



Approaches

INSTRUCTIONS

1. Identify best site with abdominal/curvilinear US probe and mark site with pen or round base of needle; avoid applying excess pressure to ensure accurate pocket size is visualized. Use vascular/linear US probe with doppler to ensure no blood vessels in identified site.
2. Open sterile OR towels package. Use light blue covering as sterile field to drop sterile supplies. Don PPE (gloves, mask, bouffant cap) & clean skin vigorously with chlorhexidine. Create sterile field over patient with OR towels or open kit and use dressing provided.
3. Anesthetize overlying skin using ~0.5cc lidocaine (SQ 25G needle) to make a wheal. **For LVP**, use 1.5 inch 20-22G to anesthetize deeper tissues with lidocaine in 10cc syringe. Use **Z-line technique** (below) and aspirate while advancing needle. Once ascitic fluid begins to fill syringe, stop advancing the needle & inject remainder of lidocaine to anesthetize the highly sensitive parietal peritoneum.

Z-line technique: Reduces risk of ascites leak by using skin as barrier. With non-dominant hand, pull skin ~2cm caudad to deep abdominal wall while para needle is being slowly inserted.

Diagnostic paracentesis instructions

a) Insert **20G two-way (pink) angiocath** through wheal at same angle as US probe and advance until slightly past when flash seen
b) Advance the catheter without moving the needle
c) Retract needle, attach 60cc syringe, and fill syringe
d) Withdraw the catheter and apply pressure with sterile gauze
e) Apply dressing using folded gauze under Tegaderm
f) Attach 18G needle to 60cc syringe and fill diagnostic tubes

Therapeutic paracentesis instructions

a) Prepare Safe-T-Centesis kit: place catheter on needle, attach syringe, and prep tubing
b) Use scalpel to make small superficial incision (enlarge PRN)
c) Advance needle/catheter while pulling back on syringe until ascitic fluid return is visualized, then advance 0.5 cm
d) Advance catheter until hubbed (only with Safe-T Centesis kit!), hold rigid needle in place
e) Retract needle, attach 60cc syringe for dx sample PRN
f) Connect tubing to catheter and puncture vacuum bottles
g) Withdraw catheter and apply gauze/Tegaderm dressing
h) Give **25% albumin (6-8g/L removed) if ≥5L removed**

DIAGNOSTIC ASSAYS: (see *Fluid Analysis* for interpretation)

Tube	Lab	Tests
Green top	Chem	Fluid albumin (send serum albumin to calculate SAAG), fluid total protein
Purple top	Heme	Fluid cell count
Blood culture bottles	Micro	Can send for aerobic & anaerobic fluid culture, clean top with alcohol and inoculate at bedside for max yield
Black top	Micro	Gram stain and culture plates
Other tests to consider:	glucose, amylase, LDH, bilirubin, triglyceride, AFB smear, mycobacterial culture, adenosine deaminase, pH, cytology	

COMPLICATIONS

- Flow stops/slows: roll patient slightly to side of para, rotate catheter, slightly withdraw catheter, flush catheter, new vacuum container
- Flash of blood in catheter: use vascular probe to avoid SQ vessels → withdraw, apply pressure, & insert new catheter at different site
- BRB return: injury to mesentery or inferior epigastrics → stop, assess for hematoma w/ US, IR or surgery consult if HD unstable
- Hypotension: likely vasovagal or fluid shift (>1500cc tap) → Trendelenburg, hydrate, and consider 25% albumin
- Bowel perforation: may lead to polymicrobial bacterascites/sepsis → surgery consult for potential laparotomy
- Fluid leak: prevent with Z-line technique or up-front dermabond → apply pressure dressing, seal w/ Dermabond or single stitch

Procedures Lumbar Puncture

INDICATIONS

Diagnostic: suspicion for CNS infection (most common), CNS malignancy/mets, SAH, CNS demyelinating/inflammatory process, or ↑ICP
Therapeutic: idiopathic intracranial hypertension, NPH, ↑ICP in cryptococcal meningitis, intrathecal meds/chemotherapy/anesthesia
Contraindications: no absolute contraindications; high risk if skin infection over puncture site, epidural abscess, ↑ICP 2/2 mass lesion or obstruction (risk of brain herniation), spinal cord tumor or AVM, thrombocytopenia (<50K) or coagulopathy (INR>1.5) of any etiology
Preparation:

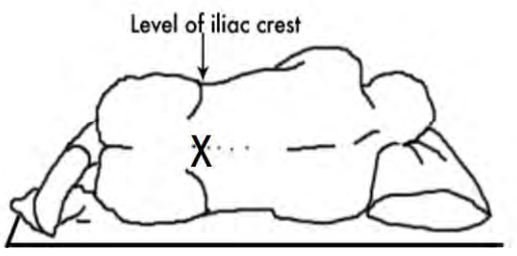
- **Time frame needed to hold AC prior to LP**: IV heparin (4-6h, PTT<35), LMWH therapeutic (24h), LMWH ppx (12h), plavix (5-7d), DOAC (3d), warfarin (3d, goal INR <1.5). OK to proceed if on SQ heparin daily dose <10,000U, ASA, or NSAIDS. If urgent: weigh risks and benefits. For details (including when to restart AC): Ellucid
- **Head CT**: only obtain if **≥1 of the following**: age >60, hx CNS disease, seizure <7d ago, immunocompromised, AMS, aphasia, cranial nerve deficit. If none of these, then 97% NPV for no mass lesion risking herniation (NEJM 2001;345:1727)

TECHNIQUE (Video: NEJM 2006;355:e12)

Equipment: LP kit, sterile towels, sterile gloves, face shield, pillows to position patient

- LP kit: 1% lidocaine (25G needle, 5cc syringe), sterile drape, iodine/chlorhex, 20-22G needle/stylet, 4 collection tubes, manometer

Positioning: proper positioning is the key to a successful and smooth LP!



- **Use L4–L5 (level of iliac crests)**, L5–S1, or L3–L4 interspaces (conus medullaris at L1–L2).
- Lateral (if opening pressure needed): place pt in fetal position (maximize neck and hip flexion), no hip/shoulder rotation; keep back parallel to edge of bed
- Upright (easier): sit on bed, head/arms rest on table, spine flexed
- To identify target: place a hand on each iliac crest, mark where thumbs meet at midline or draw line between crests. Confirm location by palpating spinous processes above/below. Ensure needle midline before inserting
- Sitting while performing LP is often easier than standing, as the needle is in your line of sight

Protocol: (JAMA 2006;296:2012)

1) Prep: sterilize and drape widely. Re-identify target with palpation (betadine will make this easier). Make lidocaine wheal w/ 25G, then inject track (aspiration before injecting, goal is **not** spinal anesthesia). Keep CSF collection tubes in order nearby. If checking pressure, have manometer connected and ready
2) Tap: check needle/stylet mobility. Bevel should face ceiling when pt is lateral. Needle angles slightly toward the head (as if aiming for umbilicus), straight at the back. Stabilize with your hand against the skin and advance with your dominant hand. Remove stylet frequently to check for CSF flow but **always keep stylet in place when advancing or withdrawing**
3) Troubleshoot: if hitting bone, partially withdraw (needle shouldn't leave skin), adjust angle, re-advance. Try space below if no luck. If patient has pain, DO NOT withdraw → ASK "where?" If pain is shooting down the left side, withdraw slightly and go slightly more to the patient's right. If hitting bone early, more likely to be superior or inferior; if hitting bone late, more likely to be too lateral
4) Measure opening pressure: once flow is established, remove stylet and connect manometer to measure opening pressure (must be in lateral decubitus position). Pt must **extend legs** to obtain accurate pressure. If performing therapeutic LP, drain until pressure normal
5) Collect: collect CSF tubes 1 to 4; if flow slows, try rotating needle or minimally advancing or withdrawing with stylet in place
6) Finish: re-insert stylet prior to needle removal (associated w/ ↓post-LP headache)

If unable to obtain LP (ie overnight) and suspicion for meningitis is high, **empirically treat while awaiting diagnostic study**

DIAGNOSTIC ASSAYS (see *Fluid Analysis*)		
Tube	**Lab**	**Tests**
1 (1mL)	Heme	CSF cell count
2 (1mL)	Chem	Total protein, glucose
3 (3-5+ mL, depending on # of tests)	Micro	Gram stain/Cx. Consider: HSV PCR, VZV PCR, CrAg, viral Cx, AFB stain, VDRL. Ask lab to save extra CSF. **If you need flow cytometry, DO NOT FREEZE CSF!**
4 (1mL)	Heme	CSF cell count (should have fewer RBCs than tube 1 unless hemorrhage)
Additional tests: cytology & flow cytometry (meningeal carcinomatosis), oligoclonal bands (MS), paraneoplastic Abs, 14–3–3 & RT-QuIC (prion dz); **can collect extra black top tubes** for these purposes; if c/f prion dz: contact materials management for instruction on special disposal of materials (highly contagious!)		

COMPLICATIONS	
Cerebral herniation (acute AMS, fixed pupils, ↑BP, brady, arrest)	Immediately replace stylet and do not drain more CSF beyond what is in manometer. STAT consult NSGY and treat with ICP-lowering agents (e.g. mannitol)
Nerve root injury	Shooting pains during procedure usually transient. Withdraw slightly and adjust position away from direction of pain. Consider dexamethasone if pain is persistent
Post-LP headache (10-30% incidence; likely 2/2 dural leak)	Onset 72h, lasts 3-14d. Give fluids, caffeine, and pain meds. No evidence for bed rest. If persistent, c/s anesthesia for epidural blood patch (65-98% success, often quick relief)
Spinal hematoma	Suspect if on AC w/ persistent back pain or neuro sx → STAT MRI → IV dex + NSGY c/s

Procedures Thoracentesis

INDICATIONS

Diagnostic: to establish etiology of ≥1cm pleural effusion visualized by US (not necessary for small effusions w/ probable alternative dx)
- pleural effusions are visible on CXR when >200mL of fluid is present (i.e. lower sensitivity)

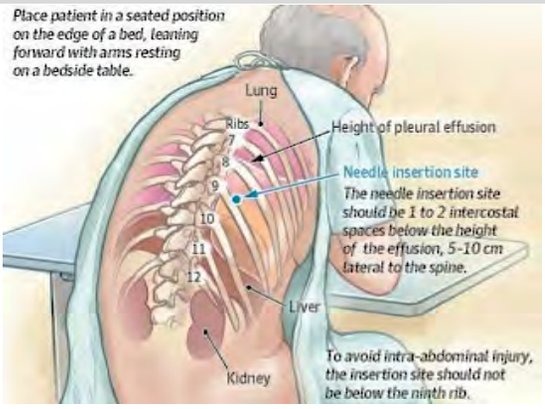
Therapeutic: large effusions → resp compromise or sx (e.g., dyspnea), hemothorax, empyema, complicated parapneumonic effusion

Relative Contraindications: *no absolute* (Chest 2013;144:456)
- Consider reversing coagulopathy (INR >1.5, recent LMWH) or thrombocytopenia (plt <50k), but no data to support
- Skin infection (cellulitis or herpes zoster) over site of entry ↑risk of pleural space infection
- Positive pressure ventilation ↑risk of PTX by 1-7% (Crit Care 2011;15:R46). US guidance associated with lower risk.

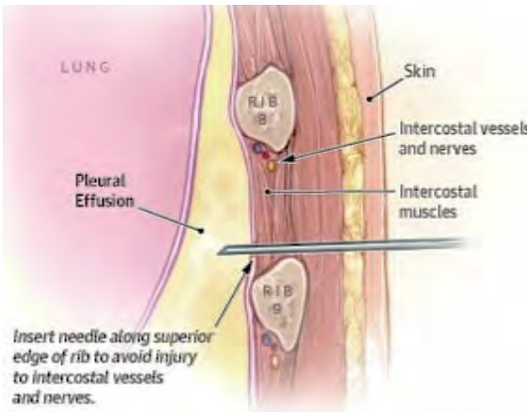
PREPARATION

- Materials: skin cleansing agent, gauze, sterile gloves/drape, hemostat, 1-2% lidocaine, 10cc syringe with 22 & 25G needle, thoracentesis kit with 18-20G over-the-needle catheter, 60cc syringe, 3-way stopcock, drainage tubing, specimen tube, evacuation container, occlusive dressing
- **At MGH: IP (p23710), Pulmonary, or IR perform thoracentesis (not AMPS). Attending MUST be present for bedside thoracentesis**

TECHNIQUE (Video: NEJM 2006;355:e16)


Place patient in a seated position on the edge of a bed, leaning forward with arms resting on a bedside table.
Lung
Ribs
7
8
9
10
11
12
Height of pleural effusion
Needle insertion site
The needle insertion site should be 1 to 2 intercostal spaces below the height of the effusion, 5-10 cm lateral to the spine.
Liver
Kidney
To avoid intra-abdominal injury, the insertion site should not be below the ninth rib.

- Position: patient at edge of bed, leaning forward with arms resting on table
- Identify: height of effusion determined by auscultation & percussion of chest wall. Use US to confirm location of effusion
  - Mark 5-10cm lateral to spine & 1-2 ICS below effusion meniscus. Lowest level recommended is 8th ICS (above diaphragm)
  - In patients who cannot sit upright → mid-axillary approach (patient supine) or posterior axillary with patient lateral decubitus
- Prep & drape: set up thoracentesis kit, put on sterile gown and gloves, sterilize patient w/ chlorhexidine, then drape
- Using 25G needle, place wheal 1% lidocaine over superior edge of the rib
- Using 22G needle, walk needle over superior aspect of the rib while intermittently aspirating and injecting perpendicular to the pleural space
- When pleural fluid aspirated, withdraw slightly then anesthetize the parietal pleura (highly sensitive) w/ 2-3cc of lidocaine. Note penetration depth
- Attach 18G over-the-needle catheter to syringe & advance over superior aspect of the rib, pulling back plunger while advancing
- When fluid aspirated, stop advancing & guide plastic catheter over needle *Catheter has valve preventing fluid or air from entering the pleural space, so may use both hands to prepare for your next step*
- Attach 60cc syringe to 3-way stopcock connected to catheter, withdraw full syringe of fluid, and put in appropriate tubes for lab & micro studies
- Attach tubing to 3-way stopcock, affixing longer tube to large evacuation container & shorter tube to the syringe. Tubing is all one-way
- Aspirate fluid slowly into the syringe and inject back into bag, never fully empty the syringe as it can lead to difficulty on repeat aspiration. Stop if: patient experiences chest pain, dyspnea, cough. Do not remove more than 1.5L fluid as ↑risk of post-expansion pulm edema



- When done, withdraw catheter while patient is humming (to avoid air entry into pleural space); cover site with occlusive dressing
- Obtain **post-procedure CXR** to assess for pneumothorax or hemothorax

DIAGNOSTIC ASSAYS (see *Fluid Analysis* for interpretation)

- Send fluid for: TP, LDH, chol, glucose, pH, cell count, Gram stain/Cx, anaerobic Cx, fungal wet prep w/ Cx
- Consider: TG (chylothorax), Cr (urinothorax), amylase (pancreatitis, esophageal rupture), ADA (TB), AFB Cx, modified AFB Cx, cytology

COMPLICATIONS

1. **Hemothorax/intercostal vessel injury**: ↑risk if inferior approach to rib or elderly (tortuous vessels). CXR, H&H. Consider chest tube
2. **PTX**: 5-20% risk; most can be monitored with serial CXR; monitor for signs of tension PTX and obtain STAT expiratory CXR; if PTX is large or patient is symptomatic and/or in distress → STAT page IP for bedside needle decompression with 16G angiocath at **5th ICS mid-axillary line** (always above nipple). A chest tube is indicated in 20% of cases → consult IP or thoracic surgery
3. **Vasovagal syncope/pleural shock**: caused by needle penetrating parietal pleura. Tx: Supportive care
4. **Re-expansion pulmonary edema**: to avoid, stop thoracentesis if cough, CP, or dyspnea occurs. Limit volume removal to <1.5L. Do not attach to vacuum. Remove fluid slowly without excessive negative pressure. Tx: O2, diuretics, and/or BiPAP

Procedures Pericardial Drain

INDICATIONS

- Pericardial effusion with tamponade physiology (or at high risk for development of tamponade physiology)
- Diagnostic or palliative drain of stable pericardial effusion

RELATIVE CONTRAINDICATIONS: *no absolute contraindications*

- Coagulopathy: INR>1.7, platelets<20, PTT>60 or on heparin gtt. Consider FFP/platelets when on call for procedure
- Effusion associated with aortic dissection or myocardial rupture, as decompression could lead to extension of injury
- Effusion associated with severe pHTN (controversial), as decompression could lead to RV dilation and acute RV failure / hemodynamic collapse (Pulm Circ 2013;3:467)

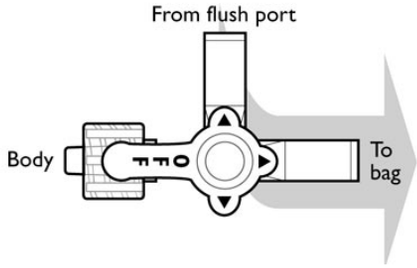
MANAGEMENT OVERVIEW: *if in doubt about management, page the Cardiology team that placed the drain*

- Pericardiocentesis does not completely evacuate a pericardial effusion. A pericardial pigtail catheter is often left in for 24-72h to allow for serial drainage, preventing re-accumulation and repeat pericardiocentesis
- Frequency of drainage depends on chronicity and size of the effusion, usually q6-q12h. Recommendations are often found in the report from the cath lab when the drain was initially placed. Typically space out as output decreases.
- **Post-procedural antibiotic prophylaxis not indicated per MGH guidelines** (MGH peri-procedural abx guidelines)
- Monitor effusion resolution and recurrent tamponade. Check serial hemodynamics/pulsus paradoxus.
- If >100cc output/d for 3d s/p placement, aggressive tx may be indicated (e.g. pericardial window, sclerosing agents, etc.)
- Consider removal of pericardial drain if <50cc output over 24h. Limited TTE. Remove with cardiology fellow/attending present

MATERIALS

- Sterile technique: sterile gloves, mask, hat
- Identify assistant (must be MD, NP, or PA)
- Sterile towels
- Chlorhexidine swabs (at least 3)
- 60cc Leur lock (screw-on) syringe (x2-3 if high output)
- New blue cap for 3-way stopcock

Heparin (10U/mL) pre-mixed syringe (in MICU/CCU/SDU med rooms)



TECHNIQUE: mask and hat required (gown is optional)

1. Open sterile towel wrap carefully. Open supplies onto sterile field. Don sterile gloves
2. Ask assistant to lift the catheter off the skin (holding end of port). Place sterile OR towels around and underneath pericardial drain. Sterilize distal exposed catheter and stopcock with chlorhex swab. Once finished, hold the recently sterilized area and take catheter from assistant to sterilize remaining distal portion. Once fully sterilized, lay the catheter down on the sterile field of blue OR towels.
3. **Ensure the stopcock is turned towards the patient**. This means the catheter line is closed.
4. Remove and throw away one blue cap (does not matter which). There will be one capped tip and one open tip
5. Sterilize open stopcock tip with iodine or chlorhex swab
6. Hold up flush port for the assistant to connect heparin syringe (syringe itself is not sterile) to open/sterilized tip. **Turn stopcock toward the remaining capped valve** (opens flush port/catheter), and assistant will infuse 2cc heparin
7. **Turn stopcock towards the patient**, remove (do not discard) heparin syringe, and connect 60cc Luer lock syringe
8. **Turn stopcock to the remaining capped valve** and slowly withdraw pericardial fluid. Gently pull back on syringe, but may require significant neg pressure. Consider different patient positions (Trendelenburg, lateral decubitus, etc.) to mobilize fluid. Patient may experience chest discomfort. Monitor hemodynamics and telemetry
9. Can stop draining once fluid flow diminishes/ceases/severe pain. **Turn stopcock towards patient** then remove syringe
10. Save/transfer pericardial fluid if needed for analysis. Otherwise discard
11. Repeat step 6 (flush port with another 2cc heparin). **Turn stopcock to the patient** (to close catheter)
12. Remove heparin syringe and attach new sterile blue cap to open flush port
13. Consider re-sterilizing distal exposed catheter and stopcock with chlorhex swab
14. Write a procedure note. **Be sure to deduct the 4cc infused heparin** (2cc from prior drainage, 2cc from current drainage) when calculating amount of fluid removed

FLUID STUDIES: typically not needed routine, serial drainage

- Gram stain and bacterial/fungal culture
- Specific viral studies/PCR
- Cytology
- AFB stain, mycobacterial culture, adenosine deaminase, IFN-gamma, or lysozyme (if considering TB pericarditis)
- Protein, LDH, glucose, red/white cell count are **not** helpful for fluid characterization

LUMBAR PUNCTURE INTERPRETATION						
Condition	**Pressure (cm H2O)**	**WBC/mL**	**Predominant cell type**	**Glucose (mg/dL)**	**Protein (mg/dL)**	**Further CSF Testing**
Normal	9–18	0–5	Lymph	50–75	15–40	N/A
Bacterial meningitis	20–50	<100 to >10k	>80% PMN	<40	100–1000	Cx, Gram stain
Viral meningitis (Enteroviruses, HSV, VZV, arboviruses)	9–20	50–1000	Lymph; early echovirus/HSV can have 80% PMN	>45; low in LCM and mumps	<200	HSV/VZV PCR, consider further viral PCR or Ab if clinical suspicion; d/w ID
Lyme meningitis	9–20	10–300	Lymph	Normal	50–100	Ab testing paired with serum ab
TB meningitis	18–30	50-300	Lymph	<50	50-300 >2000 if subarach block	MTb Cx <60% Sn, NAAT not approved by FDA, discuss w/ ID
Fungal meningitis	18–30	< 300	Lymph	<50	40–300	Fungal wet prep + Cx, d/w ID
Cryptococcal meningitis	18–30+	5–500	Lymph	<40	>45	Fungal wet prep + Cx, CrAg; d/w ID need for India ink stain
Epidural/Brain abscess	18–30	10–300	Lymph	Normal	50–400	Gram stain not sensitive
WBC correction for RBCs (i.e. traumatic tap) = measured WBC – (measured RBC / 500)						

PARACENTESIS INTERPRETATION (SEE *ASCITES*)		
	⊕ Ascites culture	**⊖ Ascites culture**
PMN ≥250/μL*	**S**pontaneous **B**acterial **P**eritonitis (SBP) (Secondary Peritonitis → polymicrobial)	**C**ulture **N**egative **N**eutrocytic **A**scites (CNNA)
PMN <250/μL	**N**on-**n**eutrocytic **B**acter**a**scites (NNBA)	Normal

Culture Negative Neutrocytic Ascites (CNNA) : has similar clinical presentation and prognosis as SBP, thus treat for suspected SBP after diagnostic PMN count without waiting for Cx (*ddx*: peritoneal carcinomatosis, tuberculosis, pancreatitis)
*Does not apply to PD pts. Effluent fluid WBC >100 w/ >50%PMNs (after >1-2 hr dwell) is concerning (see ellucid for sampling protocol)

Calculations: # of PMNs = Total nucleated cells x % of PMNsz
Correction for RBCs (RBC count >50,000/mm^3, seen in "traumatic tap") = measured PMN – (measured RBC / 250)

Clues for SBP vs. Secondary Peritonitis:
- Runyon's Criteria: if ≥2 present, ↑suspicion for secondary peritonitis: 1) ascitic total protein >1; 2) ascitic glucose <50; 3) ascitic LDH > ULN
- Fluid CEA >5 or Alk Phos >240 (92% Sn, 88% Sp for secondary peritonitis) (J Hepatol 2001;34;215)
- Consider **repeat paracentesis after 48h of antibiotic treatment:** if PMN ↓ *and* only 1 org. on prior culture, likely SBP; if PMN ↑ *and* polymicrobial growth on prior culture, then likely secondary peritonitis. Higher risk for secondary peritonitis if recent operation, trauma, or perforation

	SAAG ≥1.1g/dL (etiology related to portal HTN)	**SAAG <1.1g/dL (etiology NOT related to portal HTN)**
Fluid total protein < 2.5 g/dL	Cirrhosis	Nephrotic syndrome
Fluid total protein ≥ 2.5 g/dL	Heart failure Budd-Chiari syndrome	Pancreatitis Peritoneal carcinomatosis TB

SAAG = Serum Albumin – Ascites Albumin (from samples obtained on the same day)

PLEURAL FLUID INTERPRETATION

Transudate (due to Starling forces) vs. Exudate (due to increased capillary leak) (NEJM 2002;346:1971)

Light's Criteria: exudate if ≥1 criteria present (98% Sn, 83% Sp)*
1. **Pleural fluid protein / serum protein >0.5**
2. **Pleural fluid LDH / serum LDH >0.6**
3. **Pleural fluid LDH >2/3 ULN of serum LDH (i.e. >140)**

*Diuretics cause ~25% of transudates to be misclassified as exudates

If ≥ 1 of these, fluid is exudate with 98% Sn, 70% Sp:
- Pleural fluid protein >2.9, LDH >95, cholesterol >45

More specific criteria for confirming exudate:
- Pleural fluid cholesterol >60 (54% Sn, 92% Sp)
- Serum albumin – pleural albumin ≤1.2 (87% Sn, 92% Sp)
- Pleural NT-proBNP <2,300pg/mL (>80% Sn, >70% Sp)

- Other tests: adenosine deaminase, amylase, triglyceride, cholesterol, Gram stain/Cx, cell count, IFN-γ, NT-proBNP, pH, tumor markers
- Complicated parapneumonic effusion/empyema = ⊕ Gram stain/Cx/purulent *OR* pH <7.2 *OR* glu <60 → drainage w/ chest tube

NASOGASTRIC TUBES

Indications:
- Decompression of SBO or minimize vomiting in ileus
- Enteral feeding/med administration; charcoal admin (OD), oral contrast or colonoscopy prep (if can't take PO)
- Lactulose (hepatic encephalopathy) (if can't take PO)

Contraindications:
- Head/maxillofacial trauma, basilar skull fracture, or recent neurosurgical intervention
- Esophageal stricture or ≥grade 2 varices/recent banding (discuss w/ GI if uncertainty regarding varices/banding)

Supplies:
- NGT, lubricant/viscous lidocaine ("UroJet"), Chux, emesis basin, cup of water with ice and straw, 60mL syringe, tape
- If NGT needed for decompression: use 14 to 16 Fr Salem sump NGT (larger diameter, ↓clogging)

NGT Placement:
- Assess patency & symmetry of nares by direct visualization
- Consider topical anesthetic (e.g. 4% lidocaine) pre-treatment
- Position patient in upright "sniffing" position with neck flexed & chin to chest
- Estimate distance of NGT insertion by measuring from xiphoid process→earlobe→nose tip
- Apply lubricant/ice to tip of NGT and/or apply viscous lidocaine directly into the nares
- Insert NGT into nares along floor & apply pressure posterior & slightly inferomedial, not upward. Frequently takes troubleshooting.
- After passage of NGT into oropharynx (will feel curve & ↓resistance), have patient swallow water via straw while advancing rapidly
  - If patient excessively coughs, gags, has change in voice or dyspnea, or increased resistance, **STOP** (never force), suspect improper location (in airway or coiled), & immediately withdraw. Look in posterior oropharynx for coiling
- Advance to predetermined depth. Can insufflate air w/ 60cc syringe while auscultating over stomach for rush of air. May also see return of gastric contents. Inspect oropharynx to ensure no coiling before securing tube w/ tape or bridle if ↑risk removal (AMS)
- Confirming position: **MUST confirm placement with KUB prior to feeding/meds given risk of placement in trachea/lungs**. KUB ideally shows NGT sideport below diaphragm. Optional for KUB if bilious return when NGT for decompression (bile = stomach)

TYPES OF NGTs & USES
• Dobhoff: PO formula, meds
• 14, 16 Fr S-s: decompression

Dobhoff tube/Enteroflex: thinner, more flexible; more comfortable but ↑**risk of placement into lung**
- Requires 2-step 2-CXR placement method. Placement at MGH must be supervised by an attending
  1. Measure from nose to earlobe to mid-sternum → insert tube this distance → secure → obtain CXR
  2. If CXR shows tip (1) past carina & (2) midline → advance into stomach → repeat CXR → remove stylette once confirmed
  - Caution: *never* administer tube feeds or medications prior to confirmation. Dobhoff can pass into mainstem bronchus.

General Troubleshooting:
- If tube coiling repeatedly in oropharynx on insertion, soak tip in ice water to make tube more rigid prior to insertion
- NGT to suction should "sump" – air should audibly enter blue port and exit main port; if not: (1) flush blue port with air (never fluids), (2) flush main port with water (not NS, does not need to be sterile), (3) aspirate from main port → if not able to withdraw flush, NGT needs to be advanced vs. withdrawn (KUB can guide)
- To prevent clogging or adherence to gastric wall, NGTs should be flushed with 30cc water & air q8h. If clogged, can try methods to unclog tube as below in "Gastrostomy Tubes"
- Consider bridling tube if patient is frequently pulling out tube or if experiencing skin breakdown from security sticker. Plan ahead, as easier to place bridle prior to NG placement. Beware, very uncomfortable for the patient.

Complications (↑ with longer duration):
- GI: malposition, coiling, knotting anywhere along course of tube, nasal/GI tract perforation. ↑risk acid/stomach content reflux and aspiration → consider PPI. Chronic suction → gastritis/pressure necrosis: consider removal if grossly bloody
- Pulm: insertion into lung → inadvertent med, contrast, TF administration → PNA, pulm abscess, tracheal perforation, PTX, death
- HEENT: *nasal irritation*, epistaxis, intracranial placement, skin erosion, sinusitis, alar necrosis, tracheoesophageal fistula/perf

Removal:
If for ileus/SBO, consider removal when passing flatus or resolved n/v. Alternatively, may remove when NGT output <1L over 24h. Consider clamp trial before removing (clamp 4h, then check residual. Remove if <150cc)
- Remove tape. Flush tube w/ 10mL air or NS. Turn OFF suction & clamp. Fold Chux around tube insertion site. Gently remove tube

GASTROSTOMY TUBES

Description:

- Clear, soft, graduated tubing held in place w/ plastic mushroom-shaped ring/balloon in stomach (~3cm deeper in obese pts)
- May be replaced at bedside after epithelialized track forms (~2-4w; delayed by malnutrition, steroids, immunosuppression)
- Gastrojejunostomy (GJ) tubes have 3 access ports: G tube port, J tube port, & balloon port
- Secured with vertical Hollister device
- Venting means access port is attached to a foley bag so contents/gas can flow out as needed

Troubleshooting:

- Clogging: **only tube feeds & elixir meds should be given through J tube**
  - Attach 3cc syringe w/ warm H_2O to female Leur adaptor. Pulse plunger to force through debris. Flush w/ 30cc warm H_2O to ensure not clogged
  - Can also try Seltzer, ginger ale, Coca-Cola. If persistent, can try pancrealipase (Viokase) with sodium bicarb
- Leaking: retract balloon or mushroom back to skin level; do NOT insert larger size tube (can cause stoma to enlarge); call service who placed G tube if persistent
- Migration: can cause n/v (w/ or w/o feeds), dumping syndrome. Confirm placement w/ *tube injection study* (30-60mL gastrografin f/b KUB)
- Falling out: replace w/ similar-sized Foley or feeding tube. Obtain tube study
- Local infection: try topical abx ± antifungal before systemic (cephalexin, clinda)
- Granulation tissue: check tube size (not too long or short); tx w/ warm compresses & silver nitrate (w/ barrier cream on surrounding normal skin)

FOLEY CATHETER

Choosing Catheter: (order from Central Supply, ED, or Ellison 6 if not on floor)

- **Many contain latex**, use silicone if allergy; silicone also ↓risk CAUTI
- 2-way Foleys (drainage & balloon ports):
  16F (stock), 12F if stricture, use an ~18Fr **coudé if BPH or men >50yo** → insert curve up toward umbilicus (balloon port points towards sky) – MGH RNs can place coudés
- 3-way Foleys (drainage, balloon, irrigation ports): 20F/22F used for **continuous bladder irrigation (CBI) in gross hematuria to minimize intra-vesicular clots**

Placement:

1. Lay patient flat, prep, hold penis upright (keep on stretch while advancing)
2. Instill 10cc viscous lidocaine ("UroJet") or other lubricant syringe into urethra (men)
3. In men, insert catheter to the hub. In women, insert until urine return + 5cm more
4. Fill balloon w/ 10cc sterile H_2O only if catheter hubbed (in men) and urine return.
5. If no urine when inserted, can verify position by flushing/aspirating the catheter with a 50cc catheter-tip syringe ("GU gun"). Inability to aspirate suggests:
   a. Bladder empty and catheter sucking against bladder mucosa (instill 50-100 cc if patient does not feel like bladder is full and re-aspirate)
   b. Catheter in urethra or false passage (instill 50-100 cc – if catheter is in the urethra, what you flush in may come around catheter but you cannot aspirate)
   c. Catheter outside bladder (undermined bladder neck in pt s/p prostatectomy/TURP – this is rare)
6. If in the bladder, gently withdraw catheter after inflating the balloon until balloon engages the bladder neck
7. Secure the catheter with a little slack to the leg (attach it in the inner thigh between balloon and drainage ports so the catheter can slide down the attachment)
8. Don't forget to reduce foreskin (if not, may cause paraphimosis = **urgent problem**)

Continuous Bladder Irrigation (CBI): *consult Urology to initiate*

- Indications: gross hematuria (when you cannot see your hand through the foley due to presence of blood). DO NOT start CBI if urine has clots without manually irrigating the clots out first
- Titrate flow to "fruit punch" colored urine (should be able to see through)
- When d/c'ing, usually start with clamp trial to ensure resolution before removal

Bladder Pressure: *only done in the ICU*

Indications: concern for intra-abdominal hypertension (≥12mmHg) or frank abdominal compartment syndrome (>20mmHg)

1. Ensure patient position correlates between measurements (head position as flat as possible) and pressure transducer set-up is arranged
2. Drain bladder and clamp drainage tube of Foley
3. Inject 25cc of NS into drainage port, wait 30-60s (allows detrusor muscle to relax)
4. Connect pressure transducer to aspiration port, measure pressure at end-expiration

Special Circumstances:

Required urology catheter consults at MGH: any patient with an artificial urinary sphincter (AUS – prosthetic sphincter for men with incontinence), prostatectomy or other prostate/urethral surgery w/in past 3-4mo, known urethral stricture. *See hospital policy for full details.*

Troubleshooting:

- **Difficulty in female patient**: likely poor positioning. Place sheets under hips & place pt in Trendelenburg
- **Urethral trauma**: blood at meatus. Leave catheter in for ~3-5 days (ensure balloon is in proper place)
- **Foley is leaking**:
  - Bladder spasms 2/2 infection, mucosal irritation, overactive bladder. Start anticholinergic (tolterodine 4mg qd PRN)
  - Foley obstructed 2/2 sediment, kinked, dome of bladder, clot. Flush catheter & bladder US
  - Urethra patulous (women w/ chronic indwelling catheters)

Suprapubic Tubes:

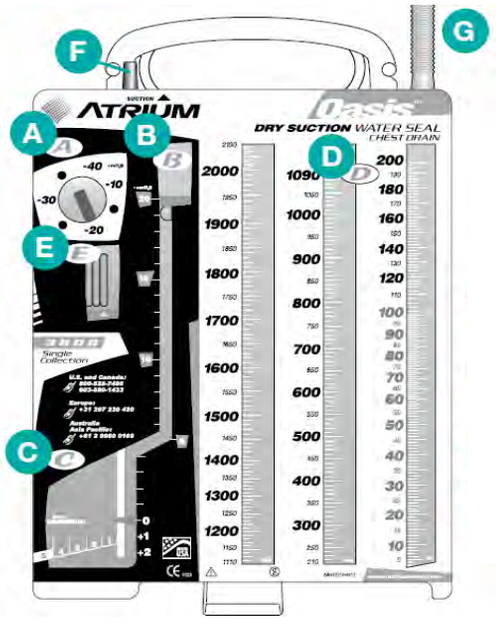
- Many different types although usually a standard Foley catheter
- Know type & size catheter, who exchanges, how exchanged, how frequently
- First exchange performed by IR. Subsequent exchanges should be performed by RNs. Urology available to assist PRN
- If need to reinsert, decompress balloon and remove indwelling SPT tube. Use Foley kit, prep area, apply lubricant to new tube, insert through tract (may have to use some force) until urine return, inflate balloon and ensure tube is mobile, attach to Foley bag
- See hospital policy

CHEST TUBES

Indications: drainage of air (PTX), blood (hemothorax), pus (empyema), or lymph (chylothorax)

Chest Tube Logistics:

- Drainage: measured by gradations in 3 columns; if significant drainage, watch for re-expansion pulmonary edema
- Daily CXR while hospitalized until removal
- Suction control: adjusts negative pressure applied to pleural space
  - Suction determined by setting on the device **[A]**, NOT at the wall; if working properly, suction verification window **[E]** orange bellows will be at triangle marker
  - **"Suction"** vs **"water seal"**: if disconnected from wall suction, it is on water seal (i.e. "to gravity") and will allow for one-way flow of air out of chest, **[E]** orange bellows not expanded



Troubleshooting:

- Air leaks: if bubbles present in the water seal chamber **[C]**, indicates air in pleural space. Higher level in chamber, greater leak. Ask patient to cough to assess for leak if bubbles are not continuous
  - Ddx: air in pleural space (parenchymal lung injury or bronchopleural fistula) vs leak in chest tube (check tubing and connections to Pleur-evac)
  - Note: "Tidaling" (movement w/ respiratory variation in water seal chamber) **[C]** is normal – i.e. *not* an air leak
- Clogging: look for debris in tube, lack of tidaling, can try "stripping the tube" by compressing it with your fingers while pulling TOWARDS the drainage system, helpful to have an alcohol prep pad for lubrication, might require tPA (alteplase) for clot or Pulmozyme (dornase) for fibrinolysis → involve IP/thoracic surgery (whoever placed tube)

Removal:

- General criteria: no active air leak, pt off positive pressure ventilation, <150cc of drainage over 24h
- Steps to removal: place on suction (-40mmHg to -10mmHg) → place on water seal → clamp trial (clamp tube with hemostat)
  - With each step, wait 4h, then obtain CXR to ensure stable or improving PTX
- After stable on clamp trial, tube should be removed during exhalation (patient humming). Large chest tubes often require surgical knot to close hole covered by occlusive dressing (xeroform, 4x4 gauze, large tegaderm) for 48h

Procedures Exposures & Needle Sticks

Please follow the steps below IMMEDIATELY in the event of an exposure to bodily fluids while on duty

1. **Stop the procedure**
2. **Immediately clean the affected area**
   - Sharp stick: wash site immediately with soap/water. Alcohol-based agents are also virucidal to HBV, HCV, HIV
   - Splash to open wound: wash site immediately with soap/water
   - Splash to eye(s): irrigate liberally for up to 5 minutes
   - Notify your department supervisor; the charge nurse is often a very helpful resource
3. **Call occupational health (OHS)**
   - Monday-Friday 7am-5pm call 617-726-2217, located at 165 Charles River Plaza (CRP) Suite 404 (4th floor)
   - If outside of normal business hours, page the on-call occupational health provider at p21272 and go to ED
   - **Have the following information available** for the OHS staff member at the time of your call:
     - Source patient: name, MRN, DOB, location, MD, diagnosis, known Hx, exposure to HBV/HCV/HIV, meds
     - Needle: brand, size, gauge, specific device/kit, device manufacturer, safety design type
4. **Test the patient for HBV, HCV, and HIV**
   - **HBV/HCV: one gold top tube**
     - Order HBsAg and HCV qualitative Ab; if patient known HCV+, also send HCV RNA
     - If using paper form (available from OA), mark with BILLING NUMBER CL00009 so pt not charged
   - **HIV: another gold top tube**
     - Order HIV 1/2 Ag/Ab (4th generation test)
     - **By law in Massachusetts** (M.G.L. c. 111, §70F), *written consent* is required to release HIV results to a third party. In the event of an exposure, since HIV status is being released to the exposed individual, *written consent* is assumed to be required
   - **Send the HIV tube to STAT lab** (results ~60min once received), send HBV/HCV tube to standard core lab

If source patient HAS capacity to consent:	If source patient DOES NOT have capacity to consent:
1. Obtain a special HIV occupational exposure consent form/lab requisition from the OA 2. Write STAT result in the comment section 3. Have the patient sign, then sign it yourself 4. Ensure form is marked with BILLING NUMBER CL00009 so patient is not charged	1. A valid and invoked health care proxy (you need paperwork!) can sign the occupational exposure consent form **OR** 2. Facility legal staff can assume temporary guardianship If the exposure occurs to a member of the *primary team*, the implication of the law is unclear, as that person is not technically a third party. Be conservative, obtain written consent anyway. If this is not possible, consider contacting HIV needlesticks fellow (p36222) or the chief residents for guidance

5. **Decide if you will initiate post-exposure prophylaxis (PEP)**

*****Post-exposure prophylaxis is most effective if started within 1-2 hours of exposure*****

- Transmission factors increasing risk: hollow-bore needle, lack of barrier protection/direct skin penetration, depth of needle penetration, increased amount of blood on the needle
- **Starting PEP is recommended if**: patient has known HIV or testing is expected to take >2 hours
  - M-F 7a-5p, PEP can be obtained at the OHS office. At all other times, you must go to the Emergency Department (page the on-call OHS provider at **p21272** to be fast-tracked in the ED for treatment)
  - **HIV fellow** can be paged to discuss PEP specifics at **p36222**

PATHOGEN	TRANSMISSION RISK	POST-EXPOSURE PROPHYLAXIS (PEP)

HIV	Percutaneous (blood): 0.3%
	Mucocutaneous (blood): 0.09%
	
	There has only been 1 confirmed case of occupational transmission since 1999 (CDC)
		PEP can vary but usually includes 3 anti-retroviral drugs:
		• 2 NRTI **tenofovir PLUS emtricitabine AND** INSTI **raltegravir**
		• 28 days of treatment recommended but optimal length unknown
		• Regimen usually well-tolerated, side effects include:
		  o Common but mild: n/v/d, fatigue, HA
		  o Rare: hepatitis, hyperglycemia, fevers, rash, pancytopenia
		• Serial testing at 6w, 12w, and 6mo if patient has HIV

HCV	Percutaneous: 1-2%	No PEP; serial testing at 4w, 12w, and 6mo if patient has HCV
AHBV	Percutaneous: 30%	Positive immune titers usually are an employment requirement Vaccine non-responders should be seen in occupational health

6. **Always file a safety report**

Logistics

Monitoring & Prophylaxis

CARDIAC MONITORING (MGH Clinical Guidelines for Cardiac Monitoring)

	Low Risk	Moderate Risk	High Risk
Monitoring	• Cardiac monitoring for diagnostic purposes only	• Continuous cardiac monitoring • May be off monitor ONLY in presence of licensed clinical personnel	• Continuous cardiac monitoring
Pt Location	General care unit	General care unit	Step-down or ICU
Travel	• No cardiac monitor • Unaccompanied	• With cardiac monitor • Accompanied by MD, PA, NP, or RN	• With cardiac monitor • Accompanied by MD, PA, NP, or RN
Example indications*	• Indicated to make dx or guide treatment • Post-op AF • Post-stroke AF • Routine syncope evaluation • Low risk chest pain syndrome	• Typical chest pain syndrome • Acute decompensated HF • Uncontrolled AF • 24 hrs s/p PPM/ICD placement and not PPM-dependent • Suspected cardiogenic syncope • Actual or risk for QTc prolongation	• Early ACS • S/p cardiac arrest • Critical care patients • Temporary PPM/pacing pads • s/p PPM/ICD and PPM-dependent • Advanced 2nd deg. HB, complete HB • Unstable arrhythmias

*See 2017 AHA guidelines on ECG monitoring for more detailed indications/monitoring duration (Circ 2017;136:e273). See *Telemetry.*

O2 SATURATION MONITORING (MGH Clinical Guidelines for O2 Saturation Monitoring)

	Low Risk	Moderate Risk	High Risk
Monitoring	• Spot check O2 sats as frequently as clinically indicated	• Continuous O2 sat monitoring • May be off monitor ONLY in presence of licensed clinical personnel	• Continuous O2 sat monitoring
Pt Location	General care unit	General care unit	Step-down or ICU
Travel	• No O2 sat monitor • Unaccompanied	• With O2 sat monitor • Accomp by MD, PA, NP, RN, or RRT	• With O2 sat monitor • Accompanied by MD, PA, NP, RN, or RRT
Example Indications	• Stable chronic respiratory disease • Post-procedure • Opioid naïve patients receiving PO narcotics	• COPD exacerbation • OSA not on CPAP • PCA use	• Acute respiratory distress • High-risk airway • NIPPV or intubation • Continuous narcotic infusion

DVT PROPHYLAXIS

	Low Risk	Moderate Risk	High Risk
Risk factors	• Ambulatory • Estimated LOS <48h • Not meeting moderate- or high-risk criteria	• Major surgery (>45min, not craniotomy, ortho, spine, or for cancer) • Acute illness; immobility w/ est. LOS >48h • H/o VTE, thrombophilia (incl. hormone tx) • Active malignancy	• Major surgery (craniotomy, ortho, spine, or for cancer) • Critical illness in ICU • 2+ moderate risk factors
Prophylaxis	Ambulation	Pharmacologic OR mechanical	Pharmacologic AND mechanical (SCDs)

- **30 / 30 / 30 Rule**
  - Pharmacologic prophylaxis: can be administered if platelets >**30**K
  - Mechanical prophylaxis: SCD boots should not be off the pt for >**30**% of the day
  - Ambulation: pts should ambulate **30**min/shift (60min/d)
- **Pharmacologic prophylaxis options**:
  - Enoxaparin (Lovenox): 40mg SC q24h; default in patients with CrCl >30 and BMI <40
  - Heparin (UFH): 5,000units SC q8h-q12h; preferred in pts with CrCl <30 or BMI >40; q8h pref. in cancer patients
  - Fondaparinux: 2.5mg SC q24h (can be used if concern for HIT)
  - Alternatives to UFH during shortage: apixaban 2.5mg PO q12h, rivaroxaban 10mg PO q24h (avoid if CrCl <30)
    - Do not use if critically ill (ICU), trauma/spinal cord injury; avoid if recent/high risk for bleeding, anticipated invasive procedure, GI/GU CA and active intraluminal lesions, Childs B/C cirrhosis or any liver disease with coagulopathy

GI PROPHYLAXIS (MGH Stress Ulcer Prophylaxis Guidelines, HCICU)

- Indications (Crit Care Med 2016;44:1395):
  - Admitted to ICU AND one of the following: 1) mechanically ventilated >48h, 2) coagulopathy (plt <50, INR >1.5, PTT >2x ULN), 3) GI bleed in the last year, 4) TBI, spinal cord injury, or burns, 5) 2+ of the following: sepsis, occult GIB >6d, steroids >60mg prednisone daily (or equivalent), ICU LOS >7d
  - HCICU Additions: 5) mechanical circulatory support 6) DAPT/triple therapy 7) scheduled NSAIDs 8) Heart and Lung transplant patients
- Prophylaxis options (PO unless contraindicated): **PPI** (omeprazole, esomeprazole, pantoprazole) or **H2 blocker** (famotidine)

Logistics Peri-Procedural Anticoagulation

General Antiplatelet & Anticoagulation Guidelines for Elective Procedures

- ASA: hold for 1 week prior if for primary prevention, continue if for secondary prevention
- P2Y12: hold clopidogrel and ticagrelor 5 days prior; prasugrel 7 days
- Warfarin: hold 5 days prior (see *Anticoagulation Management* for indications for and guidance on bridging)
- DOAC: hold 1-3 days prior, depending on agent, renal function, & procedural bleeding risk (see below for guidance for Cath Lab & IR)
- Note: NO SGLT2i for 72h prior to cases requiring cardiac anesthesia

Cardiac Cath Lab Anticoagulation Guidelines

Medication	Hold Pre-Procedure*	Resume Post-Procedure
Heparin	**Therapeutic** (>15k U/d): 1h or on call to lab **Prophylactic**: continue	4h after sheath removal; no bolus
Enoxaparin (Lovenox)	**Therapeutic** (1mg/kg): 24h; **Prophylactic** (≤60mg/d): 12h	Next morning
Bivalirudin	1h or on call to lab	4h after sheath removal; no bolus
Argatroban	1h or on call to lab	4h after sheath removal; no bolus
Dalteparin	**Therapeutic**: 24h; **Prophylactic** (≤5000 U/d): 12h	Next morning
Warfarin	5 days or INR ≤1.8	Night of cath
Apixaban, rivaroxaban, edoxaban	CrCl ≥30: ≥2 days; CrCl <30: ≥3 days	Next morning
Dabigatran	CrCl ≥50: ≥2 days; CrCl <50: ≥5 days	Next morning
Fondaparinux	CrCl ≥50: ≥4 days; CrCl <50: ≥7 days	Next morning

*Guidelines for endomyocardial biopsy differ. See MGH Cardiac Cath Lab Anticoagulation Guidelines (Ellucid)

INR Guidelines for Cardiac Catheterization

Planned Access Site	INR
Femoral artery or vein	≤ 1.8
Internal jugular vein	≤ 1.8
Radial artery	≤ 2.0
Subclavian vein	≤ 1.5
Brachial or basilic vein	≤ 2.0
Pericardiocentesis	≤ 1.5

VAD Peri-Procedural Cardiac Catheterization Guidelines

INR goal	1.8-2.5; continue warfarin
PTT goal	≤80; continue UFH pre-, intra-, & post-procedure

Cangrelor and Antiplatelet Agents

- See *ACS* for switching/bridging P2Y12 inhibitors
- Generally, prasugrel is held on day -7, clopidogrel/ticagrelor on day -5, & cangrelor is started on day -3. Cangrelor is held 1-6h pre-procedure

IR Procedures

- **NPO guidance**: NPO (no solid food; ok to take medications with sip of water) for 8h if will receive sedation (e.g. port placement, biopsies, tube placement) or if a patient-specific need for sedation
- **Low bleeding risk procedures**: paracentesis, thoracentesis, chest tube, PleurX, PICC placement/exchange/removal, non-tunneled central catheter, transjugular liver biopsy, IVC filter placement & simple removal, non-vascular catheter/tube exchange, dialysis access interventions, superficial bx/aspiration (thyroid, LN, breast, superficial bone), embolization for bleeding control
  - AC goals: INR <3, plt >20k; if cirrhosis/liver disease: INR <3, plt >20k, fibrinogen >100. **No need to hold AC**
- **High bleeding risk procedures**: tunneled central access catheter placement/removal, G- or J-tube placement, nephrostomy tube placement, biliary interventions, TIPS, solid organ/deep tissue biopsies, LP/spine procedures (Ellucid), arterial interventions/angiography, intrathoracic venous interventions (SVC/IVC), portal vein interventions, catheter-directed lysis, complex IVC filter removal
  - AC goals: INR <1.8, plt >50k; if cirrhosis/liver disease: INR <2.5, plt >30k, fibrinogen >100. AC management per table below

Medication	Hold Pre-Procedure**	Resume Post-Procedure
Heparin	**Therapeutic**: 4-6h; **Prophylactic**: 6h	6-8h
Enoxaparin (Lovenox)	**Therapeutic**: 24h / 2 doses; **Prophylactic**: 12h / 1 dose	12h
Dalteparin	24h / 1 dose	12h
Fondaparinux	CrCl ≥50: 2-3 days; CrCl <50: 3-5 days	24h
Bivalirudin	2-4h	4-6h
Argatroban	2-4h	4-6h
Warfarin	5 days or INR ≤1.8	Day after procedure; bridge if high-risk
Apixaban, edoxaban	CrCl ≥50: ≥2 days / 4 doses; CrCl <50: ≥3 days / 6 doses	24h
Rivaroxaban	CrCl ≥30: ≥2 days / 2 doses; CrCl <30: ≥3 days / 3 doses	24h
Dabigatran	CrCl ≥50: ≥2 days / 4 doses; CrCl <50: ≥3-4 days / 6-8 doses	24h

**See MGH Interventional Radiology Periprocedural Management (Ellucid)

Logistics

Senior On Encounters

CODES AND RAPID RESPONSES (Consider MGH STAT App and MGH Heart App in Partners App Catalog)

MGH CODE ROLES

- **Code leader**: Senior On
- **Code Whisperer**:
  AM = Consult SAR
  PM = Units NT
- **Pulse**: SDU JAR
- **Compressions**: Interns
- **Bring Lucas/IO**: MICU Intern

NON-SR ON TASKS

- **Confirm code status**
- Confirm/stop IV infusions
- Run tele/print strips
- Check labs, med list
- Notify attending, family

CODE TASKS

- **A**ccess (IV>>IO), **A**irway
- **B**ackboard
- **C**ode status
- **D**efibrillator, **D**rips
- **E**pi/**E**CMO/**E**mbolus **E**arly:
  - page ECMO <10min of coding
  - Consider tPA (takes 30 min to prepare)
- **F**amily (call HCP)
- **G**lucose

LABS TO ORDER

STAT ABG with K & Hgb, CBC, BMP, LFTs, lactate, T&S, coags, fibrinogen, cardiac enzymes

REVERSIBLE CAUSES (H&Ts)

Hypoxemia, **H**ypothermia, **H**ypovolemia, **H**ypoglycemia, **H**emorrhage, **T**amponade, **H**ypoxia, **T**ension PTX, **H**+ ion (acidosis), **T**hrombosis – MI/PE, **H**ypoK, **h**yperK, **T**oxin/drugs

CODE/RAPID DATA TO OBTAIN

Preceding events, code status, access, vitals, focused exam, POCT glucose, one-liner, PMH, recent procedures, last TTE, run MAR, infusions, ECG, telemetry, last labs, ABG/VBG

Call **CODE BLUE** (**x6-3333**, blue button on wall)
Call for defibrillator, backboard, ambu bag
Establish monitoring: tele, defib pads, cont O2, BP cuff

Compress 2-2.4" deep, 100-120BPM,
minimize interruptions & allow full recoil
W/o ETT: 30:2 compressions to mask vent
W/ ETT: Δ compressors q2min, breaths q6-8s, $ETCO_2$ > 10

Rhythm check as soon as pads are on
for both witnessed and unwitnessed arrest

Epi: 1mg IV/IO q3-5m **Amiodarone (VT/VF)**: 300→150 mg
Post Arrest: Pressors: if brady→levophed, if tachy→neo, bring Epi

IF INTUBATING

Prior intubations, difficult airway?, hemodynamics (RV/LV), aspiration risk (last meal), **x63333 STAT RICU**

ECMO FOR CARDIAC ARREST

Consider if possible reversible cause to arrest and ECMO a bridge to definitive treatment; at MGH, recommend contacting ECMO team <10 minutes from code initiation. STAT page "ECMO Consult MGH."

PHONE NUMBERS

ICU resource RN (x6-6718), Cardiac Access RN (x4-2677), MICU Intensivist (p26955), HCICU Intensivist (p29151), RRT/Code x6-3333

SPECIFIC SCENARIOS (see linked pages for details)

ACS

ASA 325, heparin, statin, TNG, BB
Serial ECGs, ensure telemetry
Cath lab if HD unstable, refractory CP, VT; **STEMI: x6-8282**
Discuss with interventional attending; decides on cath

BRADYCARDIA

Conduction disease, R-sided MI, vagal, med effect, ↑ICP, hypothyroidism, hypoxemia
Exam: vitals, mentation, pupils, warm/cold
Place pacing pads, establish IV access
- **Atropine** 0.5-1mg q3-5m, max 3mg (will not help in setting of CHB and Mobitz II)
- **Dopamine** 5-20mcg/kg/min
- **Epinephrine** 2-10mcg/min
- **Isoproterenol** 2-10mcg/min
- **Transcutaneous pacing** (midaz/fentanyl or ativan/dilaudid); turn to PACER → set RATE: 100BPM at first + set OUTPUT: select 100 at first
- **Transvenous pacing** (cards consult)

TACHYCARDIA

Narrow: AVRT/AVNRT, AF/Aflutter, AT, MAT
Wide: MMVT, PMVT, SVT w/ aberrancy, PPM-mediated
Medications
Narrow/reg: vagal maneuvers; adenosine; IV BB/dilt
Narrow/irregular: IV BB/dilt, amio (rhythm), digoxin (rate)
Wide/reg:
- **Amio**: 150mg →1mg/min
- **Lido**: 100mg → 50mg q5 x3 1-2 mg/min
- **Procainamide**: 20-50mg/min until hypoTN or QRS ↑50%
- Consider adenosine unless WPW

Wide/irregular:
- PMVT: amio, lido; evaluate and treat for ischemia
- Torsades: Mg 2mg, ↑HR (isoproterenol, over-drive pacing)
- AF+WPW: procainamide, ibutilide (1mg)

HYPOTENSION

Cardiogenic: MI, ADHF, BB/CCB tox, acute myocarditis, valvular dz (AS)
Distributive: sepsis, anaphylaxis, liver dz, toxin, adrenal insuff, spinal shock, sleeping
Hypovolemic: bleed, trauma, diuresis, removal w/ HD, insensible losses
Obstructive: PE, tamponade, tension PTX

PULMONARY EMBOLISM

Intermediate-High risk: PE w/ abnl VS (↑HR, ↓BP), evidence of R heart strain (TTE, ECG, or +biomarkers), central or saddle PE → PERT **x4-7378**
Order: TTE, ECG, CBC, coags, lactate, D-dimer, trop, NT-proBNP, T&S
tPA: Pulse→50-100mg/2h | follow w/ heparin gtt when PTT <x2 ULN
TNK: Pulseless→ Weight based: 30-50mg | follow with hep as above
C/I: prior ICH, isch. CVA <3mo., active bleed, CNS surg./trauma (<2-3mo)

ACUTE HYPOXEMIA

aspiration, mucus plug, PNA, pulm. edema, PE, PTX, pleural effusion

GASTROINTESTINAL BLEED

2 large-bore IV, T&S, IVF, pRBC, IV PPI 40mg. Octreotide 50mcg + CTX if portal HTN. Correct coagulopathy. RICU if hematemesis

HYPERCARBIA

↓RR: sedatives, central sleep apnea, OHS, brainstem stroke, tumor, infection, hypothyroidism
↓V_T: OSA, pleural effusion/fibrosis, obesity, kyphosis/scoliosis, abd dist, PTX, neuropathy, NMJ disorder, myopathy
↑V_D and/or ↓V_T: COPD, asthma, OSA, ILD, CHF, PNA, PE

ALTERED MENTAL STATUS

CNS: CVA, ICH, sz, infxn, PRES
Metabolic toxins: NH3, CO2, BUN, Na, glucose
Exogenous toxins: meds, drugs, w/d
Vitals: HTN/HoTN, hypoglycemia, hypoxemia
Misc: TTP, AI, hypothyroid

For seizure: lorazepam 2-4mg IV x2, midazolam 10mg IM, or keppra 20mg/kg

ANAPHYLAXIS

Epi 0.3-0.5 IM (1:1000; 1mg/mL) repeat q3-15min; other agents: benadryl 50mg, methylpred 12mg, aluberol

Beth Gay

Logistics

Post-Acute Care

POST-ACUTE CARE: post-hospital care of patients

- Largest source of Medicare regional variation. High cost growth (NEJM 2014;370:689) & risk of readmission (Health Aff 2010;29:57)
- Risk factors for use: living alone, impaired mobility, depression, comorbidity (JAMA Intern Med 2015;175:296)
- Note: do not have capability for rapid diagnostics (CT), procedures, or significant acute issues (hypoxemia, hypotension)
- Rely on Case Management, PT, & OT to help determine who qualifies for each of the below post-discharge destinations

Setting (most to least intensive)	Description	Patients / Diagnoses	Avg LOS	MD	Therapy / Ancillary Services
Long Term Acute Care Hospital (LTACH)	High intensity hospital-level care	- Tracheostomy - Chemotherapy - **≥3d ICU stay required**	20+ days	Daily MD visits	- RT - PT/OT PRN - HD
Inpatient Rehabilitation Facility (IRF, "acute rehab")	Intensive therapy for recovery of function	- Post-stroke - Spinal cord injury - Specific dx codes required	7-21 days	2-4x/week MD visits; PM&R presence	- 3+h of therapy/d (pt must be able to participate)
Skilled Nursing Facility (SNF)	"Sub-acute" rehabilitation; looks/feels like nursing home; must have 3-night hospital stay to qualify under Medicare	- CHF, PNA, UTI - Generally older patients with functional decline / unsafe at home	3-21 days	~1x/week MD visits; very limited capacity for management changes	- 1-2h of therapy/d (pt must be able to progress)
Home Health	Home-based services post-hospitalization or via PCP referral	- Wound care - IV antibiotics - Post-hospital functional decline - Home safety eval	N/A	Managed by PCP or prescribing outpatient clinician	- 4-8 PT/OT visits - RN visits as needed
Home Hospital (Home within ~8 mile radius of MGH. Separate BWH/NWH/Salem programs)	Alt. Admit Pathway: Hospital level care at home with daily labs and daily/BID IV treatments	Simple HF, cellulitis, UTI, PNA, COPD	N/A	Daily through Hospitalist team (pg 29694)	NP/PA visit x1/day, RN x2/day

SPECIAL CASES

- **Hospice**: see *Comfort Focused Care & Hospice*
  - Criteria: pt must have a terminal illness with prognosis of ≤6mo as certified by a physician. Depending on the hospice agency, pt may need to forego curative treatments (i.e., chemo, expensive antibiotics, etc.)
  - Home hospice: fully funded by Medicare. RNs visit, but patients need full-time caregiver support in the home, which can be a barrier to home hospice discharge
  - Inpatient hospice (SNF or dedicated inpatient hospice facility): room & board (~$400 per day) only covered by MassHealth, but not other insurers
  - GIP (in-hospital hospice care): fully funded by Medicare, patient must qualify
- **Long-term care**:
  - Patients residing in nursing homes with stably poor functional status and who require assistance with ADLs/IADLs, but do not require post-acute level care
  - Private pay or covered by MassHealth, but not funded by Medicare
- **Alternative programs**: if patient is in Partners ACO, discuss additional home-based care options with case manager

Logistics Bias, Patient-Directed Discharge, ICE

MANAGING MICROAGGRESSIONS & BIAS

Microaggression: a brief & common indignity (statement, action, or incident) that communicates hostile, derogatory, or negative slights to target a person or group. **Despite the name, "micro" does not speak to the severity of the impact on the target**
Bias: an attitude projecting favorable/unfavorable dispositions towards people. Bias/microaggressions can be implicit or explicit
Common examples in medicine: questioning of credentials/abilities, assumption of non-physician status, requests to change providers, belittling comments, inquiries into racial/ethnic background, inquiries into relationship status/sexual orientation/gender identity, inquiries into family/pregnancy status, comments on appearance, assumptions of religious affiliation
Upstander: a person who chooses to intervene when witnessing bias/microaggressions
Responding to microaggressions OR bias from patients (JGME 2019;11:371):
1) Prepare before the encounter:
Within your team, talk explicitly about how leadership should address the situation. For example, team leader: *"In our two weeks together, we may encounter a patient who discriminates against one of our team members. It can sometimes feel safer to have the JAR/attending address the behavior, but I want to empower you all to act if you feel comfortable. What do you think?"*
2) During the encounter:
1) Ensure the patient is stable and assess decision making capacity: if unstable, call for help to provide care. If lacks capacity (see *Consent & Capacity*), consider redirection. If stable and has capacity, proceed
2) Check your emotions and psychological safety: if you're not in a space to respond, it is OK to step out, process, ask for support
3) If you respond, address the aggression explicitly: *"I'm surprised to hear you say __." "I'm disappointed you'd say that." "What do you mean by that?" "That's frustrating to hear from a patient."*
4) Align with the patient: *"Our team is here to focus on your health." "We are all here to treat your ___."*
5) Align with your team: *"Our team is doing our best to respect you. We ask that you respect Dr. ___/me as well."*
6) Set boundaries: varies by aggression. *"I'd ask that you refrain from commenting on ___." "Please call them/me Dr.___." "Let's keep the focus on you." "We do not accommodate staff changes based on [race/ethnicity/religion/etc], Dr. __/I will be in charge of your care today." "Our institution does not tolerate that behavior/language/etc."*
7) Give space: if patient or team member is unable to continue the encounter, leave the situation with a defined time to come back. *"We are going to give you space for 30 minutes and when we come back, we can focus on your health."*

3) After the encounter:
1) Attend to emotion: if you were the target of the aggression, seek support, debrief however feels right to you. If you were a bystander, explicitly acknowledge what you witnessed, offer to support your colleague. Support can range from listening to holding their pager so they can step off the floor to decompress. Ask what they need from you
2) Discuss the encounter: once emotions have been attended to, if the target is willing, discuss as a team how the interaction went. What went well? What didn't? What would you do differently next time? Practice future phrasing together
3) Involve others: ensure attending, other providers, and unit-based leadership are aware
4) If the behavior continues: reconvene to discuss next steps as a team (attending, residents, other colleagues)

PATIENT-DIRECTED DISCHARGE (HISTORICALLY KNOWN AS AMA)

All patients have the right to discharge from treatment when they have capacity. It is the duty of the physician to obtain informed consent of discharge after discussing the risks and benefits to discharging from care. Common reasons why patients request discharge include: financial concerns, communication issues, insufficient management of pain/cravings/withdrawal, family obligations
Approach to a safe patient-directed discharge (JGIM 2013;28:1657):
1) Is the patient on section 12a or under guardianship? If yes, these patients cannot choose to leave. Involve psychiatry and security as needed to help the patient stay safely. See *Psychiatry: Agitation*. If no, proceed
2) Perform a capacity evaluation: see *Consent & Capacity*. If patient has capacity, proceed
3) Determine why the patient is motivated to leave: acknowledge their reasons for leaving, validate their emotions. Use a harm reduction lens, negotiate to meet their needs as able. If time allows, involve SW and CM to help brainstorm solutions
4) Discuss risk and benefits of leaving: ask them what they believe are the risks and benefits. Explain your recommendation. Discuss not only the immediate medical impact of their options, but the impact on their longer-term values/goals
5) Offer alternatives: if the primary recommendation of staying is rejected, offer other reasonable options. Acknowledge this may require sub-optimal care, for example, admission for IV antibiotics vs PO antibiotics with outpatient follow up or a home visit
6) Summarize recommendations, confirm understanding: Example language: *"I understand you'd like to leave the hospital today to ____. As we have discussed, remaining in the hospital will __*benefits here*___. That is my primary recommendation for you. Another potential option we discussed is _____. While it is not ideal medically, it is a reasonable option and care should align with your goals."*
7) Confirm contact information and give return precautions: coordinate follow up, remind the pt they are always welcome back for care
8) Complete paperwork: **avoid documenting "AMA" → stigmatizing and has no medicolegal benefit** (JHM 2017;12:843)

INFORMATION ON IMMIGRATION AND ICE/DHS

When should a patient's immigrant status be documented in the EHR?
NEVER. EHR can be accessed by law enforcement/immigration officials and used as evidence

What to do if ICE/DHS inquires about a patient?
If an Immigration and Customs Enforcement (ICE) or Department of Homeland Security (DHS) Agent asks for a patient or patient information, **do not provide any information about the patient**. **Immediately contact your attending and the Partners Office of General Counsel** (available 24/7; during normal business hours, call 857-282-2020. During off hours, call MGH Page Operator)

Logistics

MGH Directory

Main Number	
617-726-2000 (MGH prefix: -724, -726, -643)	
Emergency Numbers	
Senior On (Med Sr)/Bauer Room	3-1388, p22337
ED Triage Sr (ED Sr)	6-2333: x75360, p28786
Med Consult Pager (Code Backup)	p13480
RICU Team (intubation), Code Stroke	6-3333
ECMO Consult	857-310-0335, p24252 / p29151
SHOCK Consult	p11511
STEMI Team (CCL activation)	6-8282
PERT (massive PE)	4-7378
Critical Care Consult	pg 26955
IV Nurse (urgent access)	6-3631, p26571
ED Radiology (STAT imaging)	6-3050
RT (on call)	p24225
ICU Nursing Supervisor	6-6718, p25213
Poison Control (ingestion)	617-232-2120
Pharmacy	
Outpatient pharmacy (fax: 6-3789)	4-3100, pg 38121
Laboratories	
General lab info	4-LABS
Chemistry/Hematology (Core Lab)/Toxicology	6-2345
STAT Chemistry/Hematology	4-7617
Serology	4-7645
Special coagulation	4-2969
Blood gas / STAT lab – Bigelow 5	6-3856
Blood bank – Bigelow 2	6-3623
Blood bank – Lunder	8-5280
Microbiology – Bigelow 5	6-3613
Micro after hours (blood culture room)	6-7919
Parasitology	6-3861
Virology	6-3820
Surgical Pathology – Blake 3	4-1449
Immunopath (Flow, ANCA, EM)	6-8487
Cytology / Cytopathology – Warren 1	6-3980
Cardiology Studies	
Cath Lab	6-7400
Echo Lab	6-8871
Stress Lab	4-3600
Holter Lab	6-7737
EP Lab	6-5036
Pulmonary Studies	
PFTs – Cox 2	6-1200/3-9680
Sleep Study (inpatient/outpatient)	4-7426
GI Studies	
Endoscopy Lab – Blake 4	6-3732
Neurology Studies	
EEG – Blake 12	6-3640
EMG/NCS – Blake 12	6-3644
Subspecialties	
Anticoagulation (AMS)	6-2768
Boston Healthcare for the Homeless	781-221-6565
Brace Shop (White 10)	6-3248
Mass Eye and Ear Infirmary	
Page Operator	617-523-7900, 0
11th floor (Inpatient)	Above plus x2480
MEEI ED (for ENT transfers)	617-573-3431
Interpreter Services	
In Person	6-6966, p27403
Phone (Pin 1050)	617-643-3344

RADIOLOGY

- **Life Images**
  - Upload images to LifeImage and Epic: Partners Applications → Utilities → MGH Upload Image to Radiology (LifeImage) → Access LifeImage → find exam on CD/DVD → Upload images
  - Send images to MGH PACS: upload to MGH → request read
  - Retrieve images from The Cloud: ISDrequests.partners.org → file urgent ticket or request changes to existing ticket
  - Additional information:
    - Urgent reads: contact ISD **(p34188, x30003)**
    - Multiple body parts: interpretations only given for selected body parts
    - Multiple LifeImages of the same body part: upload all images → request a read only on the most recent
    - Exams will not be read if: requisition was for a different body part than the uploaded images; study >6 months old; a more recent LifeImage is available; US, fluoroscopy, or mammography

Radiology Reading Rooms	
Dodd Reception	44212
Cardiac CT	47132
Cardiac MRI	66947
Chest CT	33899
CXR Inpatient	42051
CXR Outpatient	62197
ED	41533
GI CT	65162
GI Fluoro/KUB	32605
GI MR	49919
IR (GI & VIR)	34723
Mammography	40228
MSK	40516
Neuroradiology	41931
Nuclear Cardiology	43600
Nuclear Medicine	61404
PET	66737
Vascular	47115

Technologists	
CT Blake 2	48518
CT ED	66760
ED Radiology	63050
GI Fluoro	44295
Mammography	63092
MRI ED	49867
MRI Inpatient	85692
Nuclear Medicine	68350
PET	64209
Scheduling	4XRAY
US White 2	53074